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Blood Pressure and the Incidence of Hypertension in Nulliparous and Parous Women in Relation to the Remote Prognosis of the Toxaemias of Pregnancy

BY

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THE question of the remote sequelae of the toxaemias of late pregnancy has long attracted attention. It has been stated that diseases of the vascular system, including hypertension and heart disease, and of the kidneys, eyes and brain may follow these disorders. The question is obviously one of great importance, involving not only the prognosis for future pregnancies, but also the outlook for the future health of the patient and her expectation of life. In this investigation the relation of pregnancy to blood-pressure and to hypertension is studied, in order to determine if diseases of the vascular system are caused or aggravated by pregnancy.

LITERATURE.

The relation of pregnancy and its disorders to chronic nephritis and diseases of the vascular system was studied by Theobald.[1] His conclusions were based on the study of the Registrar General's Decennial Report for England and Wales for 1911 to 1920. He showed that the mortality from Bright's disease was lower in women than in men and that the mortality rates showed the same upward and downward trends in the two sexes; that the death-rate from this cause was higher in single women than in married women in the age group 30–35; and that, while the death-rate from cerebral haemorrhage was higher in married than in single women, that from arteriosclerosis and allied disorders was higher in single than in married women. These findings led Theobald to assume that it is unlikely that toxaemia of pregnancy causes chronic nephritis or circulatory disease.

On the other hand, many authors have shown that pre-eclamptic toxaemia and eclampsia are followed by hypertensive disease. Browne and Dodds,[2] in a follow up study of 400 patients in 589 pregnancies, showed that hypertension followed pre-eclamptic toxaemia in 50.9 per cent of

cases, and followed eclampsia in 60.8 per cent. They concluded that the older the patient the greater her parity, the higher the blood-pressure during pregnancy, the longer the duration of the illness, the greater seemed to be the liability to the ultimate occurrence of residual hypertension. In their conclusions, however, they suggest "that patients who develop residual hypertension after pre-eclamptic toxaemia and eclampsia have a familial tendency to the disease which pregnancy has merely revealed and the onset of which the pregnancy has hastened, so that it sets in at an earlier period than it would otherwise have done."

Chesley and Somers,[3] in a study of the sequelae of eclampsia in 169 cases, found a statistically significant increase in the incidence of hypertension in these patients compared with the female population at large, after correction for age distribution. They point out that, among other factors, the higher the first observed blood-pressure in pregnancy, the more likely is the hyperpiesia to persist.

These findings by Chesley and Somers and similar findings by other authors may be interpreted in two ways. It may be that pre-eclamptic toxaemia and eclampsia do actually cause hypertension. Or, it may be that patients who suffer from these disorders have already a tendency to hypertensive disease. Such patients have an unstable blood-pressure liable to fluctuation and the general level of their blood-pressure tends to increase with advancing years. This would explain the greater incidence of hypertension following toxaemia in older patients.

Isenhour, Kuder and Dill[4] studied the mean blood-pressure and the incidence of hypertension in 900 parous and 900 nulliparous women. Demonstrable difference was not found in either of the two groups and it is concluded that if hypertension occurs as a sequel to a toxaemic pregnancy, it is not a result of the toxaemia, but that the patients who develop hypertension would have done so in any case, and in spite of the pregnancy, and that the hypertension did not occur any earlier because of the pregnancy.

A similar opinion is held by Dieckmann[5] who states that "for a number of years I have believed that pre-eclampsia and true eclampsia do not cause permanent vascular or renal pathology and that the patient who has such pathology would have had it eventually if she had never been pregnant. I believe that this latter group of patients has a predisposition to hypertensive arterial disease by inheritance or by physical or mental instability. . . . These patients may have hypertension at first during pregnancy, but after several pregnancies or a period of years the blood-pressure remains elevated. . . . The incidence of vascular disease rises rapidly with increasing age."

Hypertension is an extremely common condition. This was shown by Robinson and Brucer[6] in a study of normal blood-pressure based on a statistical study of 10,883 persons, on a study of 5- to 10-year continuous records of 500 persons, and on an appraisal of mortality and general blood-pressure levels. These authors conclude that slightly more than 40 per cent of the adult population is either actually or potentially hypertensive. Normal blood-pressure does not exceed 120 mm. Hg. systolic or 80 mm. Hg. diastolic and a blood-pressure exceeding 120/80 for 10 years or more is abnormal and is an infallible sign of incipient hypertension. The mortality-rate rises progressively with an increase in systolic or diastolic blood-pressure.

The mistake has frequently been made in the past of considering the mean or average to be the same as the normal blood-pressure. Robinson and Brucer's findings

expose the obvious fallacy of this. Any group of blood-pressure readings in adults will contain a number of hypertensives and the greater the age of the patients, the higher will be the blood-pressure of those with hypertension and the greater the number of those in whom incipient hypertension has become revealed.

Results of the Investigation.

The 1,956 patients comprising this series had all attended the Gynaecological Out-patient Department of the Obstetric Unit at University College Hospital and the Gynaecological Out-patient Department of the Watford Peace Memorial Hospital. To collect material for the present paper routine estimation of blood-pressure was begun in every patient attending these clinics. The blood-pressure is taken by the auscultatory method in the arm with the patient seated. The records used in this paper are those of consecutive cases, but some have been excluded for the following reasons: Every patient who was pregnant or in whom there was a suspicion of pregnancy at the time of examination was excluded. One patient who was referred to the clinic on account of hypertension was not included. A number of others were excluded because the *data* recorded were inadequate—in some the blood-pressure had not been taken and in others essential details such as the number of children were lacking. In any case in which the blood-pressure seemed abnormally high it was retaken after a period of rest.

The records were first divided into those of nulliparae, comprising 915 patients, and of patients who had borne children, comprising 1,041 patients. The patients were further divided into 10-year age groups up to the age of 49. Patients aged 50 and over were considered in a single group as their numbers were insufficient to classify them in 10-year groups.

First, a general comparison was made between the blood-pressures of nulliparous and parous women in the various age groups. The results are given in Table I.

Table I.

Mean Blood-pressures in all Age Groups.

Age group		Total	Systolic blood-pressure (mm. Hg.) Mean	S.D.*	Diastolic blood-pressure (mm. Hg.) Mean	S.D.*
10 to 19	Nulliparous ...	82	119.4	11.0	76.3	9.6
	Parous	3	109.0	49.6	69.0	4.9
20 to 29	Nulliparous ...	401	119.3	15.7	76.2	11.3
	Parous	208	121.8	14.1	77.4	10.8
30 to 39	Nulliparous ...	274	126.9	15.5	78.5	12.3
	Parous	364	126.0	15.0	79.0	13.2
40 to 49	Nulliparous ...	105	134.9	19.3	85.0	12.1
	Parous	275	134.7	22.3	85.5	13.0
Over 50	Nulliparous ...	53	152.7	30.9	91.6	17.0
	Parous	191	155.1	30.7	93.2	16.0

* Standard deviation.

Two important facts emerge from the figures given in Table I. There is no statistically significant difference between the blood-pressures of nulliparous and parous women in any age group. Indeed it is remarkable how, in every age group, the

cases, and followed eclampsia in 60.8 per cent. They concluded that the older the patient the greater her parity, the higher the blood-pressure during pregnancy, the longer the duration of the illness, the greater seemed to be the liability to the ultimate occurrence of residual hypertension. In their conclusions, however, they suggest "that patients who develop residual hypertension after pre-eclamptic toxaemia and eclampsia have a familial tendency to the disease which pregnancy has merely revealed and the onset of which the pregnancy has hastened, so that it sets in at an earlier period than it would otherwise have done."

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40 to 49	Nulliparous ...	105	134.9	19.3	85.0	12.1
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Over 50	Nulliparous ...	53	152.7	30.9	91.6	17.0
	Parous	191	155.1	30.7	93.2	16.0

* Standard deviation.

Two important facts emerge from the figures given in Table I. There is no statistically significant difference between the blood-pressures of nulliparous and parous women in any age group. Indeed it is remarkable how, in every age group, the

mean blood-pressure of nulliparous and parous women differs by no more than a few mm. of mercury. It can be concluded, therefore, that pregnancy has no effect on the level of blood-pressure. There is also a progressive rise of blood-pressure, i.e. of the mean blood-pressure, with age. These figures are closely comparable with those of Isenhour, Kuder and Dill.[4] Table II is modified from their paper for comparison with the results in the present series.

140/90. These results are given in Table III.

Study of Table III reveals that there is no statistically significant difference in any age group between the proportions of nulliparae and multiparae with blood-pressures over 120/80 or over 140/90. In the age group 20–29, the difference between nulliparous and parous women with blood-pressures over 120/80 is 5.5 per cent. The Standard Error is 7.2 and thus the result

TABLE II.
(Modified from Isenhour *et al.*[4])
Mean Blood-pressure in all Age Groups.

Age group		Total	Systolic blood-pressure (mm. Hg.) Mean	S.D.*	Diastolic blood-pressure (mm. Hg.) Mean	S.D.*
20 to 29	Nulliparous ...	200	119.6	9.5	73.2	7.1
	Parous	200	117.8	10.0	73.4	9.3
30 to 39	Nulliparous ...	200	124.3	13.4	75.7	9.1
	Parous	200	125.1	11.4	77.9	8.9
40 to 49	Nulliparous ...	200	133.5	20.4	81.9	11.2
	Parous	200	135.5	15.4	82.7	9.5
50 to 59	Nulliparous ...	200	144.4	24.6	87.3	13.4
	Parous	200	148.0	23.6	86.8	11.0
60 to 69	Nulliparous ...	100	158.0	30.8	90.9	13.0
	Parous	100	161.9	23.2	89.6	11.8
Over 50	Nulliparous ...	300	148.9		88.5	
	Parous	300	152.6		87.4	

* Standard deviation.

The incidence of hypertension in nulliparous and parous women was next determined. As there is still disagreement about what constitutes normal blood-pressure, the figures were analysed from two points of view. First, accepting the work of Robinson and Brucer,[6] the number of patients in whom both systolic and diastolic blood-pressure reached or exceeded 120/80 mm. of mercury was estimated and their percentage of the total estimated. A similar procedure was carried out in patients in whom the systolic and diastolic blood-pressure reached or exceeded

is not significant. The same applies in all the other age groups. Age groups 30–39 and over 50 show differences in the over 120/80 group of 6.2 per cent and 7.3 per cent, but the Standard Errors are 6.1 and 6.6 respectively. Also, in the over 50 group, there is a difference of 8.1 per cent between nulliparae and parous women with blood-pressures over 140/90, but here the Standard Error is 11.9

Table III also shows that with advancing age there is a gradual increase in the proportion of patients with blood-pressures over 120/80 and over 140/90 but this

TABLE III.

Patients with Blood-pressure over 120/80 and over 140/90.

Age group		Total	Blood-pressure over 120/80		Blood-pressure over 140/90	
			Total	Per cent	Total	Per cent
10 to 19	Nulliparous ...	82	23	28.0	0	0
	Parous	3	1	33.3	0	0
20 to 29	Nulliparous ...	401	101	25.2	16	4.0
	Parous	208	64	30.7	9	4.3
30 to 39	Nulliparous ...	274	117	42.7	23	8.4
	Parous	364	133	36.6	27	7.4
40 to 49	Nulliparous ...	105	61	58.0	20	19.0
	Parous	275	162	59.0	58	21.1
Over 50	Nulliparous ...	53	38	71.7	21	39.6
	Parous	191	151	79.0	91	47.7

increase affects parous and nulliparous women equally, and cannot therefore be attributed to the effect of pregnancy.

Finally, the results were analysed to show whether the number of pregnancies had any influence on the level of the blood-pressure. This was carried out for age groups 20–29, 30–39 and 40–49, and the results are given in Table IV. It is shown that parity has no effect on blood-pressure.

DISCUSSION.

It has been shown that pregnancy has no ultimate effect on the mean level of the blood-pressure or on the incidence of hypertension at any age. Nor does pregnancy cause a latent tendency to hypertension to be revealed earlier in a patient's life. The great majority of children are born to women between the ages of 20 and 39. Table I shows that in the age groups

TABLE IV.

Influence of Parity on Blood-pressure in Parous Women.

Age group		Total	Systolic blood-pressure (mm. Hg.)		Diastolic blood-pressure (mm. Hg.)	
			Mean	S.D.*	Mean	S.D.*
	Total	208	121.8	14.1	77.4	10.5
20 to 29	Para 1	136	119.4	13.5	77.6	11.4
	Para 2	53	122.0	13.5	76.7	2.9
	Para 3 and more	19	113.5	10.8	76.6	9.5
	Total	364	126.0	15.0	79.0	13.2
39 to 49	Para 1	179	128.0	18.5	80.6	13.5
	Para 2	104	123.1	14.0	77.5	13.6
	Para 3 and more	81	127.7	18.5	78.2	14.0
	Total	275	134.7	22.0	85.5	13.0
40 to 49	Para 1	85	133.0	19.0	85.1	11.7
	Para 2	91	137.9	22.6	86.9	14.9
	Para 3 and more	99	133.2	23.3	86.4	11.9

* Standard deviation.

20–29 and 30–39 there is a close correspondence between the blood-pressures of nulliparous and parous women, while Table III shows that in the age group 30–39, the incidence of hypertension is actually lower in parous women than in nulliparae, though the difference is not sufficiently large to be statistically significant.

It seems certain that if toxaemia of pregnancy causes persistent hypertension, this would be revealed in the present series. Further evidence on this point is furnished by the finding that the number of children born has no effect on the level of the blood-pressure in any age group. It has often been stated that childbearing throws a strain on the vascular system which increases with each succeeding pregnancy. This is not shown to be the case in regard to hypertension.

Toxaemia of pregnancy may thus be regarded as a temporary disorder, specifically associated with pregnancy and leaving of itself no permanent vascular lesion. Factors such as a familial or inherent tendency to hypertension may modify the severity of the toxaemic condition and such factors may be detectable before pregnancy occurs, or in the early months, or may not become apparent for months or years after. In any case, whether toxaemia has occurred or not, the ultimate level of blood-pressure in a parous woman will be the same as it would have been if she had never been pregnant. The length of time taken for the effect of the toxaemic process on the vascular system to pass off after pregnancy is uncertain, though it is known that the renal lesion of toxaemia may take as long as 2 years to heal. Browne and Dodds[2] described a case in which albuminuria persisted for 2 years after delivery and then cleared up completely. It is therefore unwise to attempt to arrive at the remote prognosis of a case of toxaemia of pregnancy until at least a year has elapsed since delivery. Many fallacies in the remote prognosis of toxaemia have arisen because patients have not been followed up for a sufficiently long time.

Patients who have had toxaemia of pregnancy may thus be divided into two groups. The first group consists of patients in whom the vascular system is normal and in whom there is no tendency to hypertension. These patients have toxaemia because of some unknown factor, acquired as a result of pregnancy and operating mainly in first pregnancies. After delivery their blood-pressure returns to normal, and the prognosis for future pregnancies will be good. The second group consists of patients in whom there is a tendency to hypertensive vascular disease. These patients would have developed hypertension eventually even if they had never been pregnant. The prognosis for future pregnancies will depend on the level of blood-pressure at the time conception occurs. Browne and Dodds[7] showed that if the blood-pressure at the start of pregnancy was 150/100 or over, the prognosis for the foetus was poor, and in their series only 32 per cent of the children of such mothers survived.

Toxaemia of pregnancy is a condition which is dangerous to mother and child. Constant vigilance is necessary in the antenatal period in order to detect its early signs. The findings in the present series, however, make it appear doubtful whether any treatment including even the premature interruption of pregnancy, is likely to affect the remote prognosis for the mother.

Should pregnancy be terminated to prevent the development of chronic hypertension in the mother? The fact that the patient who has hypertension for more than 4 weeks during pregnancy is more likely to develop chronic hypertension is undoubted but is, if the conclusions in this paper are correct, evidently due to the fact

that women who are potential hypertensives develop hypertension at an earlier period in pregnancy than others do, and the hypertension is therefore of longer duration. It is evident that there is no justification for the premature termination of pregnancy with the purpose of making the mother less liable to permanent hypertension. Pregnancy may still be interrupted if there seems to be a risk of eclampsia or after the foetus is viable, i.e. at the end of the 37th week, if this is considered necessary, owing to the severity of the toxaemia, to save the foetus from death *in utero*.

Does pregnancy aggravate hypertension already existing when pregnancy starts? If the conclusions of this paper are correct it is evident that it does not. Not only is there no increased incidence of hypertension in parous women compared with nulliparae, but there is no significant difference between the mean blood-pressures of the two groups at any age. A patient who has chronic hypertension of severe degree at the onset of pregnancy runs a considerable risk of losing her baby, but there is no evidence in our series that pregnancy has any deleterious effect on the remote prognosis for the mother.

Summary and Conclusions.

1. An analysis has been made of the blood-pressures of 1,956 women. Of these, 915 were nulliparous and 1,041 parous.

2. Statistically significant differences could not be found between the mean level of blood-pressure in nulliparous and parous women at any age.

3. There was no statistically significant difference in any age group between the percentages of nulliparous and parous women with blood-pressures over 120/80 or over 140/90.

4. The number of pregnancies had no demonstrable effect on the mean level of blood-pressure in parous women.

5. Pregnancy does not cause chronic hypertension. The level of blood-pressure in parous women is the same as it would be if they had never been pregnant.

6. Pregnancy does not aggravate a tendency to hypertension, neither does chronic hypertension develop earlier in parous women.

7. Though hypertension is a common remote sequel of toxaemia of pregnancy it is not caused by the toxaemia. Patients who develop hypertension following a toxaemic pregnancy would have done so if they had never been pregnant. A tendency to hypertension often contributes to the severity of toxaemia.

8. Toxaemia of pregnancy may be regarded as a temporary disorder closely associated with pregnancy and leaving of itself no permanent lesion.

9. There is therefore no justification for terminating a toxaemic pregnancy prematurely in order to protect the mother from chronic hypertension.

10. There is no evidence that pregnancy permanently aggravates hypertension already existing when pregnancy starts. There is therefore no justification for terminating an early pregnancy in a patient who has essential hypertension.

Our thanks are due to Mr. W. J. Martin of the Department of Epidemiology and Vital Statistics, University of London, for his invaluable help with the statistical work embodied in this paper.

The Frequency Distribution Curves of blood-pressure relative to Tables I and IV will be found at the end of this paper (Figs. 1 to 8). In each case the ordinate represents the number of patients whose blood-pressure falls within the 10 mm. groups in the abscissa. For reasons of space a single number only is given in the abscissa in each case; for example, "120" represents the group whose blood-pressure falls between 120 and 130 mm. of mercury

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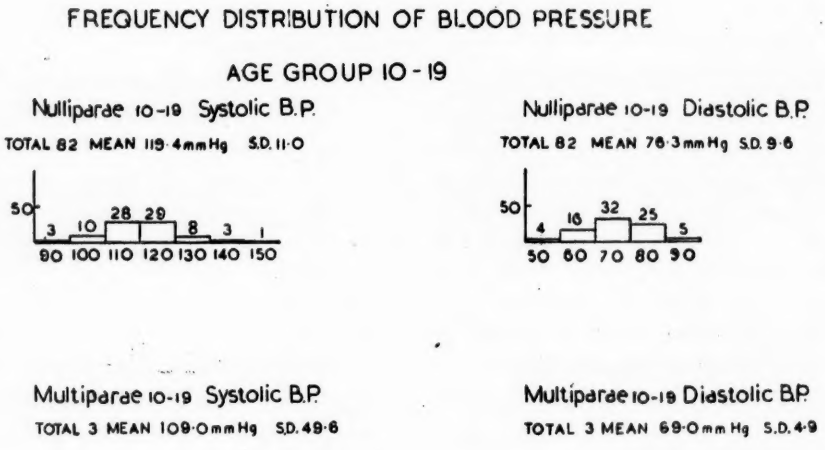

FREQUENCY DISTRIBUTION OF BLOOD PRESSURE
AGE GROUP 10 - 19
Nulliparae 10-19 Systolic B.P.
TOTAL 82 MEAN 119·4mmHg S.D. 11·0
50
3 10 28 29 8 3 1
90 100 110 120 130 140 150
Nulliparae 10-19 Diastolic B.P.
TOTAL 82 MEAN 76·3mmHg S.D. 9·6
50
4 16 32 25 5
50 60 70 80 90
Multiparae 10-19 Systolic B.P.
TOTAL 3 MEAN 109·0mmHg S.D. 49·6
Multiparae 10-19 Diastolic B.P.
TOTAL 3 MEAN 69·0mmHg S.D. 4·9

Figure.1.

FREQUENCY DISTRIBUTION OF BLOOD PRESSURE

AGE GROUP 20-29

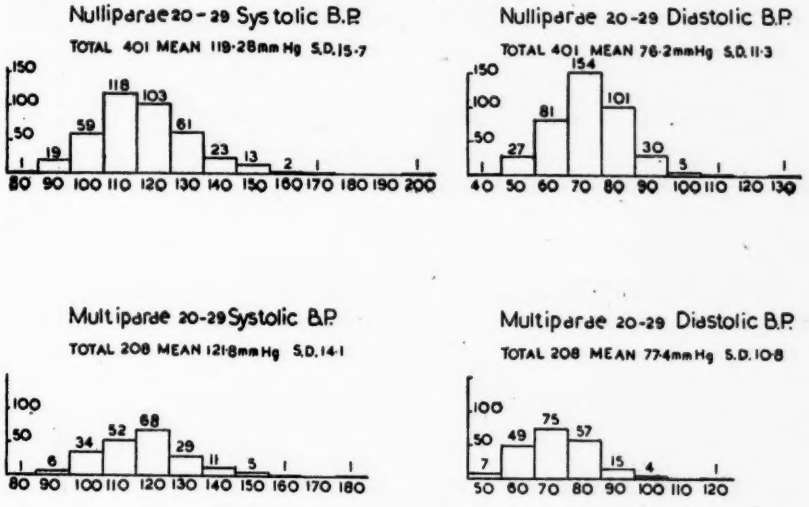

Nulliparae 20-29 Systolic B.P.
TOTAL 401 MEAN 119·28mm Hg S.D. 15·7
Nulliparae 20-29 Diastolic B.P.
TOTAL 401 MEAN 76·2mmHg S.D. 11·3
Multiparae 20-29 Systolic B.P.
TOTAL 208 MEAN 121·8mm Hg S.D. 14·1
Multiparae 20-29 Diastolic B.P.
TOTAL 208 MEAN 77·4mm Hg S.D. 10·8

Figure 2.

FREQUENCY DISTRIBUTION OF BLOOD PRESSURE

AGE GROUP 30-39

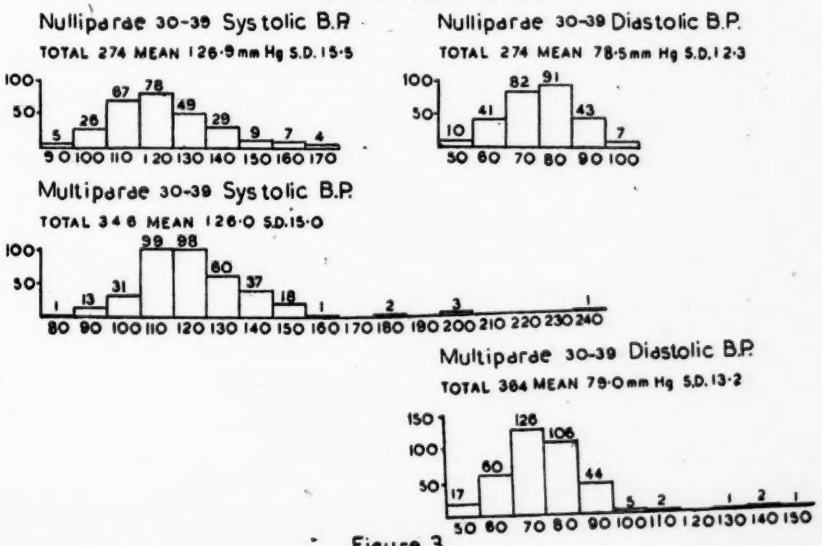

Nulliparae 30-39 Systolic B.P.
TOTAL 274 MEAN 126·9mm Hg S.D. 15·5
Nulliparae 30-39 Diastolic B.P.
TOTAL 274 MEAN 78·5mm Hg S.D. 12·3
Multiparae 30-39 Systolic B.P.
TOTAL 346 MEAN 126·0 S.D. 15·0
Multiparae 30-39 Diastolic B.P.
TOTAL 364 MEAN 79·0mm Hg S.D. 13·2

Figure. 3

FREQUENCY DISTRIBUTION OF BLOOD PRESSURE

AGE GROUP 40-49.

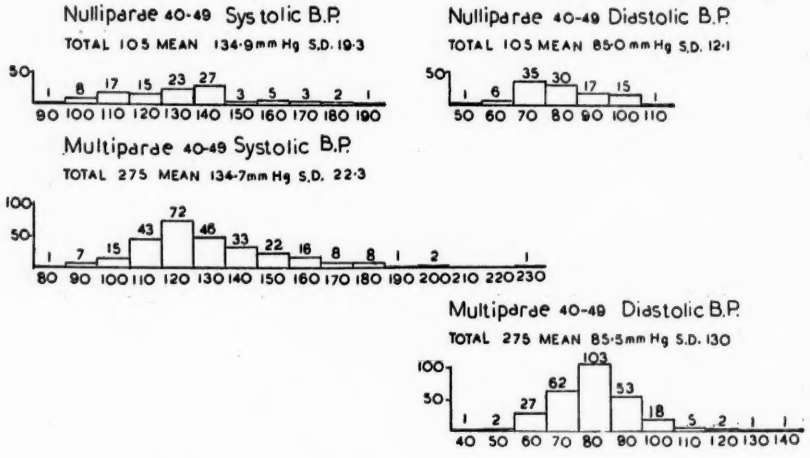


Figure 4.

FREQUENCY DISTRIBUTION OF BLOOD PRESSURE

AGE GROUP OVER 50

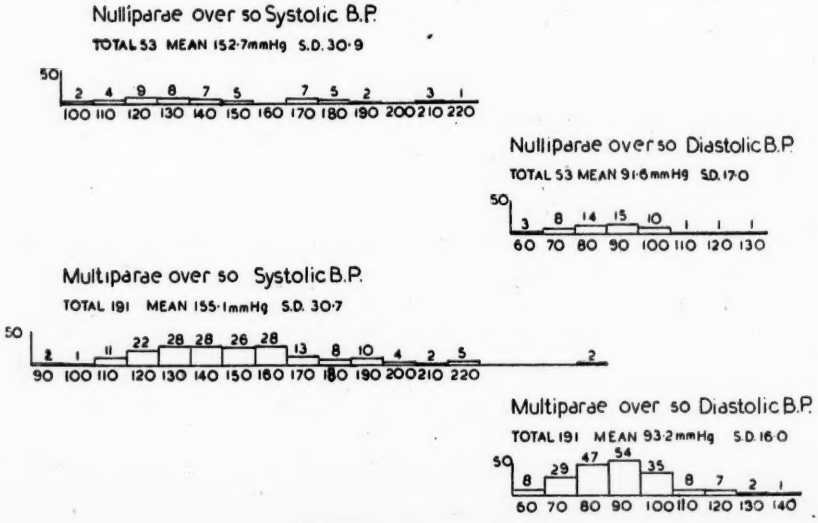


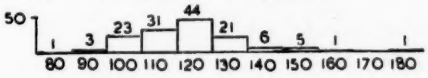
Figure 5

EFFECT OF PARITY ON BLOOD PRESSURE

MULTIPARAE 20-29 TOTAL 208

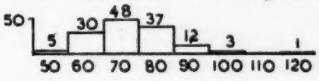
Para 1 Systolic B.P.

TOTAL 136 MEAN 119·4mm Hg S.D. 13·5



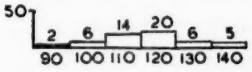
Para 1 Diastolic B.P.

TOTAL 136 MEAN 77·6 mm Hg S.D. 11·4



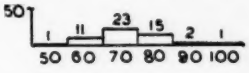
Para 2 Systolic B.P.

TOTAL 53 MEAN 122·0 S.D. 13·5



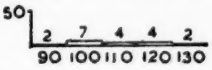
Para 2 Diastolic B.P.

TOTAL 53 MEAN 76·7mm Hg S.D. 2·9



Para 3 and more Systolic B.P.

TOTAL 19 MEAN 113·5mm Hg S.D. 10·8



Para 3 and more Diastolic B.P.

TOTAL 19 MEAN 76·6 mm Hg S.D. 9·5

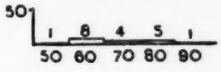


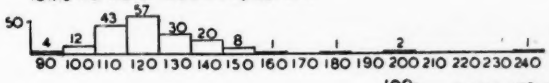
Figure 6.

EFFECT OF PARITY ON BLOOD PRESSURE

MULTIPARAE 30-39 TOTAL 364

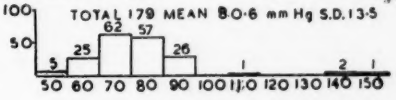
Para 1 Systolic B.P.

TOTAL 179 MEAN 128·0 mm Hg S.D. 18·5



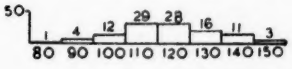
Para 1 Diastolic B.P.

TOTAL 179 MEAN 80·6 mm Hg S.D. 13·5



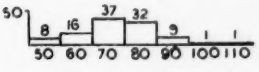
Para 2 Systolic B.P.

TOTAL 104 MEAN 123·1 mm Hg S.D. 14·0



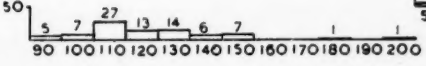
Para 2 Diastolic B.P.

TOTAL 104 MEAN 77·5 mm Hg S.D. 13·6



Para 3 and more Systolic B.P.

TOTAL 81 MEAN 127·7 mm Hg S.D. 18·5



Para 3 and more Diastolic B.P.

TOTAL 81 MEAN 78·2 mm Hg S.D. 14·0

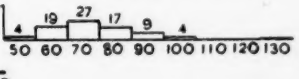


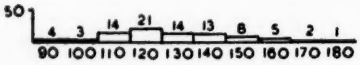
Figure 7.

EFFECT OF PARITY ON BLOOD PRESSURE.

MULTIPARAE 40-49 TOTAL 275

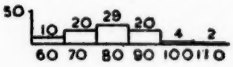
Para 1 Systolic B.P.

TOTAL 85 MEAN 133·0 mm Hg S.D. 19·0



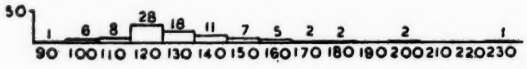
Para 1 Diastolic B.P.

TOTAL 85 MEAN 85·1 mm Hg S.D. 11·7



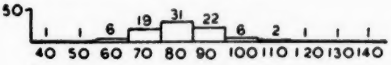
Para 2 Systolic B.P.

TOTAL 91 MEAN 137·9 mm Hg S.D. 22·6



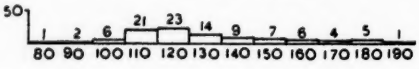
Para 2 Diastolic B.P.

TOTAL 91 MEAN 86·9 mm Hg S.D. 14·9



Para 3 and more Systolic B.P.

TOTAL 99 MEAN 133·2 mm Hg S.D. 23·3



Para 3 and more Diastolic B.P.

TOTAL 99 MEAN 86·4 mm Hg S.D. 11·9

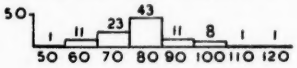


Figure 8.

Renal Failure in Obstetric Practice

BY

G. SHEDDEN ADAM, M.B., B.S., F.R.C.S., M.R.C.O.G.

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RECENT contributions to medical literature have, in many instances, related directly or indirectly to the problem of renal failure.

It may be timely, therefore, briefly to review the whole question of renal failure as encountered in obstetric practice, to apply our knowledge of renal physiology and of diuretic substances to this problem, to record certain illustrative case histories and to indicate such methods of treatment as have been found of value.

Partial or complete suppression of urine may develop as a complication of pregnancy or the puerperium from a variety of causes. It is a recognized, though not a particularly frequent, complication of eclampsia and, of course, is likely to develop in the less frequently encountered acute glomerulonephritis when this occurs during pregnancy or the puerperium.

Renal failure may follow a transfusion reaction resulting from an unrecognized Rh-incompatibility, and it is now apparent that pregnant and puerperal women are especially liable to be involved in such reactions.

Quite apart from the transient oliguria of obstetric shock, there is evidence that urinary suppression may develop as the result of maternal birth trauma, and the pathological and clinical features in these cases are said to have much in common with the "compression syndrome" as described in recent observations on air-raid casualties.

The association of renal failure and concealed accidental haemorrhage is also recognized. Symmetrical cortical necrosis of the kidneys, though rare, is another cause of severe and often fatal anuria, usually but not invariably associated with pregnancy, and preceded, in many cases, by a concealed accidental haemorrhage.

More remote possibilities are extensive renal infarction, bilateral ureteral obstruction and Clostridium welchii septicaemia.

RENAL PHYSIOLOGY.

Studies of renal physiology show that, although glomerular filtration is essential for urine formation, it is supplemented by tubular excretion of certain substances. Absorption, however, is the chief function of the renal tubules; water and various constituents of the body being reabsorbed from the glomerular filtrate if the plasma content of these constituents falls below a certain concentration; in other words urine is derived from blood plasma by the selective work of the kidney.

Clinically, urinary suppression is likely to develop (in the absence of circulating diuretic substances) if the systolic blood-pressure falls below 75 mm. Hg. because of the fall in hydrostatic pressure in the glomerular capillaries. This is no longer sufficient to overcome the osmotic pressure exerted by the plasma-proteins and the resistance offered by capsular pressure.

The plasma osmotic pressure has been estimated as approximately 30 mm. Hg. and the capsular pressure as approximately

15 mm. Hg., so that the effective hydrostatic pressure within the glomerular capillaries must exceed 45 mm. Hg. for filtration to occur.

Within certain limits any change in the arterial pressure will be reflected in an altered filtration pressure and, therefore, in the rate of filtration. Nevertheless, while a marked fall in blood-pressure usually results in a diminution or suppression of urine, an increased arterial pressure is not necessarily accompanied by an increased output.

Reduction in effective glomerular filtration to the point of urinary suppression also occurs when the pressure within the ureter is raised to about 30 mm. Hg. above atmospheric pressure.

Determination of the rate of urine excretion is normally affected primarily by regulation of the fraction of water reabsorbed by the tubules, rather than by regulation of the filtration rate itself. This concentration of the glomerular filtrate is, at least in part, controlled by the anti-diuretic hormone of the posterior pituitary lobe which, passing into the bloodstream, acts by accelerating the reabsorption of water from the tubular urine.

The study of diuretic substances and their effect on renal physiology is obviously important in considering the management of renal failure as encountered in obstetric practice. The simplest form of diuresis is that which follows the ingestion or parenteral administration of sufficient water to produce a relatively abrupt blood dilution. The increased urinary output in these circumstances is considered to be due to the temporary inhibition of the secretion of the anti-diuretic pituitary hormone.

An increased urinary output may also be brought about by temporarily increasing the concentration of electrolytes in the blood. The majority of electrolytes occurring in normal plasma are threshold substances inasmuch as they are retained in the body when the plasma level has fallen and are freely excreted when the plasma level is raised. The excretion of those electrolytes present in excess of the normal plasma levels is usually accompanied by a diuresis. Thus, while the ingestion of an isotonic sodium chloride solution is not followed by an increased urinary output, the parenteral administration of a hypertonic sodium chloride solution causes a marked diuresis in the normal subject.

Again, effective diuresis in healthy persons, and in some patients exhibiting an oliguria, may be obtained by the intravenous administration of substances such as sodium sulphate which are not, to any appreciable extent, reabsorbed by the tubular epithelium.

The increased urinary output in these circumstances is probably due to the interference with the reabsorption of water from the glomerular filtrate exerted by the osmotic pressure or ionic concentration of these substances.

Diuresis may also occur as the result of a sudden disturbance of the osmotic equilibrium of the plasma. This is the basis of the intravenous glucose (dextrose) therapy (using a 25 per cent or 30 per cent solution) used in the management of eclamptic patients.

Titus,[1] Deickmann[2] and others considered that, if more glucose could be introduced into the body over a short period of time than could be burned, stored as glycogen or polymerized, the excess would, theoretically, be excreted in the urine, resulting in a polyuria.

Effective diuresis was obtained in eclamptic patients by the intravenous administration of 1,000 c.c. of a 20 per cent glucose solution (200 gm.) over a period of 30 to 50 minutes, especially if the treatment were repeated in 8 to 12 hours' time.

Examination of urine collected over a

26 hours' period of such treatment, however, demonstrated that comparatively little or no glucose was excreted in the urine, but that there was a constant increase in the chloride excretion.

The explanation of this, it was suggested, lay in the fact that the osmotic equilibrium of the plasma could be restored more easily by the excretion of chlorides which exert a greater osmotic pressure than glucose; 1 grm. of sodium chloride exerting 5 times as much osmotic pressure as 1 grm. of glucose.

Reference will be made to this form of therapy in the case reports to be quoted.

Eclampsia.

The excretion of water in the normal pregnant patient tends to be faulty, and in severe pre-eclampsia and eclampsia oliguria (excretion of less than 600 c.c. of urine in 24 hours) occurs in 75 per cent to 85 per cent of cases; anuria (absence of urine for 12 hours or more) occurs in 1 per cent to 3 per cent of cases.[2] Zangemeister, from his observations on urinary suppression in eclampsia and pre-eclampsia, considered that this was most marked during the convulsive stage and concluded that both the convulsions and the oliguria depended on the same cause. Spickman, on the other hand, formed the impression that the oliguria of eclamptic patients was especially common after delivery and was usually accompanied by a lowered blood-pressure.

Mortality statistics for eclampsia indicate that the death-rate is in the region of 44 per cent if the oliguria lasts for more than 24 hours, and 90 per cent if it persists in spite of treatment.[2] The significance of the fact that many of these cases do not die of uraemia (c.f. symmetrical cortical renal necrosis where the oliguria may persist for 8–12 days before death from uraemia occurs) will be considered subsequently.

There is reason to believe that spasm of the intrarenal arterioles with glomerular ischaemia is a more likely cause of the urinary suppression in eclampsia than simple oedema of the kidney. The glomerular lesion is peculiar to eclampsia and the changes described are not necessarily irreversible; although hyalinization of some glomeruli, due to complete obliteration of capillaries, undoubtedly occurs in some cases. The power of recovery of the glomeruli is evident in the spontaneous diuresis which usually follows the successful management of the eclamptic patient, and in the uneventful course of subsequent pregnancies in many instances.

While a spontaneous diuresis may be anticipated, such a development is by no means assured, and there is evidence that a therapeutically induced diuresis at any earlier stage may favourably influence the prognosis for reasons other than those directly related to the urinary output. A digression, therefore, from the consideration of actual renal failure may be permitted. If it be accepted that the convulsions, the coma, the tachycardia and pyrexia, and possibly the visual disturbances of eclampsia, are due to cerebral anoxaemia resulting from oedema of the brain, then any effective method of combating and reducing the cerebral oedema must inevitably reduce that element in the mortality resulting from repeated convulsive seizures, deep coma, exhaustion and cardiac failure. There is, of course, nothing intrinsically new in this conception; it is rather to the method of inducing a diuresis sufficient to relieve the cerebral oedema that attention has been directed in recent years.

The effective diuresis which will often follow the intravenous administration of hypertonic solutions of glucose in eclamptic patients has already been referred to. The greater degree of success which has been achieved with this measure in contrast to

that obtained by other diuretic or dehydrating agents may be due to the co-incidental excretion of abnormally retained chlorides. It is well known that chloride retention in eclampsia is an aggravating feature of the condition, being due, probably, to retention of sodium with resultant retention of chloride, rather than to failure of the kidneys to excrete chloride.

Dieckmann[2] found that the urine from eclamptic patients on admission was relatively low in chlorides but that, after a diuresis had been established, whether spontaneously following delivery or by the intravenous administration of hypertonic glucose solution, the concentration of sodium chloride increased despite the increased urinary output.

Our own experience in the use of this diuretic agent in the management of both pre-eclamptic and eclamptic patients has been encouraging. Originally reserved for those cases exhibiting a severe oliguria, it is now given as part of the routine treatment of eclampsia. Although it failed to alter the course of the fatal illness in 1 case of fulminating eclampsia, we have, on several occasions, felt it to be a life-saving procedure.

In the moderately severe case of eclampsia in which there has not been any grave risk to the mother's life nor anuria, the routine use of hypertonic glucose solutions intravenously has appeared to hasten the convalescence and to abolish almost entirely that mental retardation which so often delays complete recovery from the post-eclamptic state. It has proven especially useful in those eclamptic patients, usually but not necessarily manifesting an oliguria, in whom the convulsions have been brought under control and measures taken, often successfully, to induce labour, but in whom there is no lessening in the depth of their coma.

It has been our experience that, in all but the milder cases, the intravenous administration of the hypertonic glucose solution has to be repeated, and in this connexion a urinary output averaging less than 30 c.c. per hour is regarded as an indication for repeating the treatment. The initial diuresis, while effective (600–900 c.c.) is often short-lived, whereas the improved urinary output which usually follows the second or third treatment tends to be maintained, probably because it coincides with a general recovery from the eclamptic state.

Judicious selection of available veins is necessary, commencing at the more distal sites on the limb. Thrombophlebitis around the point of cannula, so troublesome when glucose solutions are given by the slow drip technique, is obviated by the more rapid rate of infusion.

The following case report is illustrative of the response obtained in eclamptic patients:

CASE 1.

Mrs. J. J., a previously healthy primipara, aged 20 years, was admitted to hospital at 6.15 a.m. on May 15th, 1944, as a case of intrapartum eclampsia.

The urine, on admission, was scanty (56 c.c. only obtained) and "solid" with albumin, the blood-pressure was 190/110 mm. Hg. and the patient was comatose and subject to frequent eclamptic convulsions.

Fortunately labour was well advanced and it was possible to deliver the patient of a living female infant 3 hours later. Nevertheless, the convulsions persisted, the coma deepened, and the pulse-rate rose to 136 beats per minute.

Hypertonic glucose (1,000 c.c. of a 25 per cent solution) was given by the intravenous route at 11.30 a.m. and 480 c.c. of urine were obtained by catheterization an hour later.

Convulsions ceased at 2.30 p.m. but the patient remained deeply comatose. In view of this fact a further 1,000 c.c. of 25 per cent glucose solution were given intravenously at 7.30 p.m. This was followed by a satisfactory diuresis (600 c.c.), but on the following day (May 16th) the urinary output

had fallen again to a critical level and the patient was still comatose, with a pulse-rate of 140 beats per minute, and a temperature of 104°F. The urine contained a " half " deposit of albumin.

Another 1,000 c.c. of 25 per cent glucose were therefore given intravenously and the urinary output again improved. The relative diuresis, moreover, was maintained on this occasion, the amount of urine secreted averaging just over 90 c.c. per hour and containing only a " deposit " of albumin.

In spite of this the patient was still comatose on the following day (May 17); this being the 3rd day of the coma, and the prognosis appeared gloomy. (Blood urea estimation 126 mg. per 100 c.c. blood.) However, towards evening the coma lightened, and the patient recognized and spoke to her husband.

From this time the clinical picture was one of steady improvement. Complete consciousness was present the following day (May 18th), the urinary output continued at a satisfactory level, the blood-pressure had fallen to 130/80 mm. Hg., the albumin had disappeared from the urine and the blood urea had fallen to 36 mg. per 100 c.c. of blood by May 20th. The patient and her baby were discharged from hospital in good health and spirits on the 21st day after admission.

This form of treatment may also be used with advantage in certain cases of pre-eclampsia with oliguria as illustrated by the following case record:

CASE 2.

Mrs. M. K., a multipara aged 37 years, was referred for hospital treatment on June 17th, 1944, when 39 weeks pregnant, because of the development of severe pre-eclamptic manifestations; headaches, gross oedema of the face, hands and ankles, a blood-pressure of 230/150 mm. Hg. and a " two-thirds " deposit of albumin in the urine, which had been diminished in volume. The patient was dyspnoeic and generally distressed.

Routine treatment was commenced, including the 6-hourly administration of ammonium chloride in 10 grain doses as a diuretic. Nevertheless, the urinary output for 24 hours ending at midnight on June 18th was only 614 c.c., and for the next 12 hours only 224 c.c. of urine were secreted. Hypertonic glucose was therefore given at 7.30 p.m. (1,000 c.c. of a 25 per cent solution) intravenously, and 1,530 c.c. of urine were passed during the next 12 hours.

The patient gave birth to a living female infant at 6.15 a.m. on June 20th but, on catheterization 6 hours later, only 90 c.c. of urine were obtained, which was " solid " with albumin.

A further 1,000 c.c. of 25 per cent glucose solution were therefore given intravenously. This was followed by a satisfactory diuresis (1,110 c.c. of clear urine over a period of 1½ hours following the commencement of the intravenous therapy).

On June 21st the oedema was appreciably less, the urinary output was 1,950 c.c., and the blood-urea was 42 mg. per 100 c.c. blood. The blood-pressure, however, was 200/118 mm. Hg. and was still 190/110 mm. Hg. 2 weeks later.

In spite of the persistent hypertension (suggesting previous vascular disease) the marked improvement in the general appearance and demeanour of this woman was both rapid and striking.

That such improvement might well have occurred following delivery without specific treatment to establish a diuresis must be admitted, but the impression was formed that, in a patient verging so closely on the eclamptic state, recovery without convulsive phenomena had been facilitated by the hypertonic glucose therapy.

ACUTE GLOMERULONEPHRITIS.

Acute glomerulonephritis, *per se*, is an uncommon complication of pregnancy, and the incidence (including recurrent attacks), in a large series of cases recently reviewed,[3] was found to be as low as 0.05 per cent. If, however, acute nephrosis (or the nephrotic form of acute glomerulonephritis) is included, these conditions may resemble pre-eclampsia or even eclampsia to such an extent that at times the correct diagnosis cannot be made until after the confinement.

On the other hand, the contention that such differences as exist in the clinical and pathological manifestations of the acute

diseases of the kidney on the one hand, and the toxaemias of pregnancy on the other, are purely incidental to the pregnancy, has little to support it.

What, then, are the criteria necessary for a diagnosis of acute glomerulonephritis complicating pregnancy? A recent focal infection, often streptococcal, the persistence of red blood cells in the urine for a period longer than a week, nitrogen retention and the persistence of oedema and albuminuria after delivery indicate, in a previously healthy patient, that the condition is likely to be one of acute nephritis (possibly of the nephrotic type) rather than a simple pregnancy toxaemia.

Should the decision rest upon autopsy evidence, careful examination of sections from the kidney may be necessary. Endothelial proliferation in the glomeruli with leucocytic infiltration would favour acute glomerulonephritis.

While both conditions are comparatively rare, the diagnosis, on purely clinical grounds, between acute nephritis complicating pregnancy and symmetrical cortical necrosis of the kidneys may present difficulties. The latter condition, however, is characterized by the late development of uraemic manifestations (resembling surgical anuria), a transient haematuria and an associated accidental antepartum haemorrhage in many cases.

Acute glomerulonephritis must therefore be considered in the investigation of any obstetrical case exhibiting an oliguria or anuria not obviously due to other causes.

The following case history, for example, illustrates the difficulty in distinguishing the syndrome of pre-eclampsia from that of acute glomerulonephritis.

CASE 3.

Mrs. J. W. was a primipara, aged 19 years, who subsequently gave a history of recent attacks of tonsillitis. The pregnancy had been uneventful until the 30th week, when she made her 6th antenatal visit on August 3rd, 1942, complaining of swollen ankles and headaches. Her blood-pressure, previously 130/90 mm. Hg., had risen to 180/112 mm. Hg., and her urine, previously clear, showed a "seven-eighths deposit" of albumin. She was admitted to hospital as a case of pre-eclampsia and the appropriate treatment commenced. Microscopic examination of the urine revealed many red blood cells, hyaline and granular casts.

On August 4th, 1942, the patient suffered an accidental antepartum haemorrhage, subsequently came into labour and expelled a premature and stillborn infant. Throughout the day she was lethargic, drowsy and vomiting; and the blood urea was 74 mg. per 100 c.c. of blood. Only 60 c.c. of urine, containing "one-third deposit" of albumin, were secreted.

On August 5th, 1942, little more than 90 c.c. of urine were secreted, and it became solid with albumin on boiling. The blood urea was 98 mg. per 100 c.c. of blood, the oedema of the lower limbs was still marked, the vomiting was less.

On August 6th, 1942, the urinary output rose to 720 c.c., the blood-pressure had fallen to 150/95 mm. Hg. and the albuminous deposit to one-sixth, with a corresponding improvement in the general condition.

Subsequently, the daily urinary output varied from 75 c.c. to 1,050 c.c. per day, the blood urea was 65 mg. per 100 c.c. of blood on August 10th and, on August 13th, some red blood cells and a few casts were still present on microscopic examination of the urine.

A very relevant aspect of the management of acute diseases of the kidney complicating pregnancy is the place of therapeutic induction of abortion or of premature labour.

Although it is characteristic of these conditions that the haematuria, oedema and albuminuria persist in spite of delivery, it is nevertheless true that the tendency towards faulty water elimination, oedema, albuminuria and abnormal fat metabolism observed even in normal pregnancy is likely to aggravate the course of an acute nephritis or nephrosis.

Wegner[3] reported that, in a series of 10,596 women whose pregnancies were reviewed, there were 10 cases of acute glomerulonephritis and 3 of acute nephrosis, an incidence of 0.056 and 0.025 per cent respectively. In every case the renal condition appeared to be aggravated as the pregnancy advanced and the mortality rate was 33.3 per cent for each condition.

Renal Failure following Transfusion Reactions due to Incompatibility involving the Rh Factor.

Unfavourable reactions following the transfusion of whole blood to recently confined patients, with evidence of intravascular haemolysis, icterus, and suppression of urine, have been noted with concern from time to time, especially as these reactions had usually occurred after transfusions given under the most favourable conditions, and after apparent compatibility had been established by the usual methods of blood typing and cross matching.

A cause of incompatibility reactions which may lead to a fatal anuria, and one of especial significance in obstetric practice, is the Rh property of human blood, and the recent (1940) work initiated by Landsteiner and Wiener[4] in this connexion is now universally recognized. Especially important is the appreciation of the fact that, in obstetric practice, it is not necessary for a woman to be given a second transfusion before incompatibility reactions involving the Rh factor can occur. There seems little reason to doubt that the conception of isoimmunization in the human body by the Rh factor is a correct one, and the evidence on this score is now well known.[5, 6]

When the original work on the Rh factor was published, it soon became apparent that it would have especial implications when applied to obstetric practice, and the study of renal failure in this field calls for further consideration of the factors involved. Renal failure following the transfusion of incompatible blood is dependent on intravascular haemolysis and is unlikely to follow simple agglutination of the donor cells.[7]

Only about 30 per cent of immune sera will haemolyse as well as agglutinate red cells containing the corresponding agglutinogen,[8] but it is important to note that, even when agglutination occurs *in vitro*, intravascular haemolysis may occur *in vivo*. Thus, although haemolysis never occurs *in vitro* when Rh positive cells are incubated with sera containing Rh antibodies, there is abundant evidence (*[9] et al.*) that severe intravascular haemolysis may follow the transfusion of Rh positive blood to a recipient possessing anti-Rh agglutinins in her serum.

The titre of the incompatible agglutinins in the recipient's plasma and the rate of transfusion appear to determine the mode of destruction of the donor's cells.[8]

Fairley,[10] pointed out that haemoglobin liberated by intravascular haemolysis may be dealt with in three different ways:

(*a*) It may be absorbed by the reticuloendothelial system and converted to bilirubin which is then discharged into the blood-stream and excreted by the liver. This is probably the only mechanism necessary when the haemolysis is slight.

(*b*) When the haemolysis is of greater degree, part of the haemoglobin is broken down intravascularly and haematin is liberated. This combines with serum albumin to form methaemalbumin which may, if in sufficient concentration, be recognized on spectroscopic examination.

(*c*) Some haemoglobin is excreted by the kidneys, but apparently[7] a concentration of 135 to 180 mg. of haemoglobin per 100 c.c. of plasma (approximately equivalent to the rapid haemolysis of 60 c.c. of blood) is necessary for this to occur, although once

commenced haemoglobinuria may continue at lower plasma haemoglobin levels.

If the urine is alkaline most of the haemoglobin will be present in the form of oxyhaemoglobin and the urine will be red.

If the urine is acid or neutral methaemoglobin will be formed; acid haematin will be deposited in the renal tubules and casts of this substance may be found in the urine, which is dark in colour.

Following intravascular haemolysis, some degree of renal failure may occur with oliguria and a progressive increase in the blood urea estimations.

Baker and Dodds[11] expressed the opinion that the renal insufficiency in these cases was due to blockage of the renal tubules with acid haematin, a relatively insoluble compound which is formed in urine of high acidity and salt concentration. They were able to prevent the onset of renal failure in rabbits, to whom haemoglobin solutions had been given intravenously, by alkalizing the urine. Baker[12] further elaborated this point in 1939.

This conception, however, has been opposed by others, including De Navasquez,[13] who believes that the anuria is the result of a diminished blood flow through the renal glomeruli, and by DeGowin *et al*[14] who expressed the opinion that, in man, blockage of the renal tubules is insufficient in many cases to account for the degree of renal failure and postulated tubular damage by some "nephrotoxic factor" as the cause of the anuria.

Clinically, signs of uraemia may not be apparent until the 3rd or 4th day after the transfusion of incompatible blood. Thereafter a critical phase develops between the 6th and the 12th days, during which time the patient may become comatose and die, or may start passing large quantities of urine and recover.

A reduction in the incidence of severe or fatal anuria following intragroup transfusion reactions in pregnant or puerperal women may be expected as a result of the wide interest which has been aroused in the clinical application of knowledge relating to the Rh factor. It is now unlikely that the husband of a woman who had given birth to an infant suffering from erythroblastosis foetalis would inadvertently be allowed to act as a blood donor to his wife even though his blood were compatible by the usual standards.

Nevertheless, the possibility exists of antibody production in the mother's serum of insufficient titre to cause erythroblastosis foetalis but sufficient to cause a troublesome reaction if the patient should be transfused with the husband's blood.[6] Until such time as all laboratories concerned with pretransfusion tests for obstetric cases are equipped to carry out the special cross-matching technique[15] for demonstrating Rh incompatibility, the husband should not be regarded as a suitable donor for pregnant or puerperal patients.

The following case record illustrates very clearly the type of haemolytic transfusion reaction, almost certainly involving the Rh factor, encountered prior to the publication of Landsteiner's work on this subject:

CASE 4.

Mrs. M. R., aged 29 years, had had 3 normal infants, but her 4th pregnancy had terminated in the birth of a stillborn hydropoid infant in March 1937.

On September 25th, 1939, she was delivered of a stillborn macerated foetus which manifested the ascites and generalized oedema so characteristic of this form of erythroblastosis foetalis. The placenta, too, was hyperplastic and oedematous.

A pronounced hypochromic anaemia had been present during the latter weeks of the pregnancy; on September 21st the erythrocytes numbered 2,530,000 per c.mm. and the haemoglobin value was estimated as 30 per cent. Although there was no postpartum haemorrhage at the time of confinement, it was felt that the patient's convales-

cence would be hastened and her general condition improved by a blood transfusion during the puerperium.

On September 28th, therefore, the blood groups of the patient and her husband were investigated and both were found to belong to Group O. Direct cross-matching tests were satisfactory. On September 30th 600 c.c. of citrated blood were given into the patient's cubital vein; the donor being the husband.

A rise of temperature to 102°F. followed within a few hours of the transfusion and the patient complained of some tightness in the chest. The next day, October 1st, she was deeply jaundiced and catheterization produced only 15 c.c. of concentrated acid urine.

Following Baker's suggestion that renal failure in these circumstances might be averted by effectively and rapidly alkalizing the urine, efforts were directed towards this end. An alkaline compound prepared commercially for intravenous use was administered by this route, and an alkaline mixture was given by mouth every 2 hours.

In an endeavour to ascertain the cause of the reaction the blood of both the recipient and the donor was retyped and cross matched, but no agglutination could be detected after the patient's serum and the donor's red cells had stood in the incubator for 50 minutes. (This can now be explained[16] by the fact that the transfused cells would have temporarily absorbed most of the recipient's serum agglutinins.)

On October 2nd, the patient's condition was much the same; the jaundice was still present and the urinary output was only 21 c.c. for the 24 hours. During the afternoon, 500 c.c. of a 25 per cent glucose solution were given intravenously as an empirical procedure.

On October 3rd the jaundice was less intense and the urinary output was 112 c.c., the urine being now alkaline in reaction. A blood count revealed 2,300,000 red cells per cubic millimetre and a haemoglobin value of 27 per cent.

On October 4th 196 c.c. of urine were secreted and, on subsequent days, the 24 hours' urinary output was as follows: October 5th, 168 c.c.; October 6th, 660 c.c.; October 7th, 1,800 c.c.; October 8th, 1,290 c.c.; October 9th, 1,560 c.c.; October 10th, 2,250 c.c.; October 11th, 3,110 c.c.

The jaundice had disappeared by the end of the 1st week after the transfusion, and the blood count gradually improved with iron therapy.

Obstetric Shock—Maternal Birth Trauma and Concealed Retroplacental Haemorrhage.

Whatever views may be held on the aetiology of obstetric shock, the factors responsible for the oliguria do not differ materially from those encountered in non-obstetric or surgical shock.

In these cases, the renal failure is usually transient (assuming recovery from the shocked condition) and may rightly be attributed to the profound circulatory disturbance. The oligaemia and vascular hypotonia lead to a reduced blood volume passing through the glomeruli, and to a diminished filtration pressure respectively.

The oliguria usually responds to those measures normally put into operation (including the intravenous administration of blood serum) to combat the shock. If the patient does not respond to these measures and death occurs, it will not be because of the renal failure which is primarily symptomatic.

A form of renal failure is, however, occasionally encountered in obstetric practice in which the element of maternal birth trauma appears to play an important aetiological *rôle*. In other cases, the renal sequelae have followed a concealed (retroplacental) accidental haemorrhage.

As Young[17] has pointed out, there is the same clinical sequence irrespective of whether the tissue damage occurred as the result of a prolonged and difficult labour or developed as a consequence of a retroplacental haemorrhage.

1. There is the initial tissue damage.
2. In severe cases, there is shock which may or may not be fatal. In those patients who survive, there develops:
3. Evidence of renal failure with oliguria

and a rising blood urea which usually reaches its peak between the 5th and the 9th days, and which is followed either by death or by an increasing diuresis and eventual recovery.

A further point of interest lies in the close resemblance between these two clinical states and the "compression syndrome." Instances have been reported[18] in which patients, though successfully passing through a period of shock after a prolonged and difficult labour, subsequently developed renal failure and died; and most obstetricians will recall similar happenings in their experience.

In the reported cases, however, the histological lesions in the kidney closely resembled those described by Bywaters and Beall in 1941,[19] and more fully by Bywaters and Dible in 1942.[20]

These consist of degenerative and necrotic lesions of the tubular epithelium and the presence of pigmented casts in the lumina. A raised serum potassium level and myohaemoglobinuria were also present. The matrix of the casts was considered, on histological grounds, to be composed, not of red corpuscles, but of desquamated epithelial cells, and the pigmentation was attributed to the excretion from the blood-stream of myohaemoglobin.

Whether a "compression syndrome" comparable with that described by Bywaters and Beall exists in obstetric practice, as has been suggested, awaits the accumulation of further clinical biochemical and pathological *data*.

Although clinical details only are available, reference may be made to the following case report:

CASE 5.

Mrs. R. S., aged 21 years, a previously healthy primipara, was admitted to hospital on July 27th, 1940, as a case of failed forceps. Labour had been in progress for 2 days and, although dehydrated and exhausted, the patient was not appreciably shocked. Catheterization on admission produced only 60 c.c. of concentrated blood-stained urine.

Delivery was effected by a lower segment Caesarean section. Post-operative treatment followed the usual lines and 2,000 c.c. of normal saline were given by an intravenous drip during the next 12 hours to combat the dehydration to which the initial oliguria was attributed.

On July 28th the patient's condition was generally satisfactory during the morning but she became confused and restless towards evening. Although fluids were being taken readily by mouth, only 115 c.c. of urine were secreted during the day.

On July 29th the blood urea was 113 mg. per 100 c.c. of blood and the oliguria persisted. A small blood transfusion (350 c.c.) was given during the day from a compatible female and unrelated donor.

On July 30th the patient was comatose, urine was not secreted and uraemic vomiting and twitching developed. Death occurred during the day but consent for autopsy could not be obtained.

The one feature common to all air-raid casualties exhibiting renal failure, not obviously due to other causes, was the evidence of compression of muscle tissue for varying periods, but usually from 6 to 9 hours. Some degree of muscle necrosis was also present but often to a limited degree.

It has been shown by Baetjer[21] that when muscle fibres are injured their permeability increases and intracellular ions, such as potassium, are rapidly lost. (Increase in serum potassium levels was a constant finding in these cases.)

The injured muscle fibres also liberate a pigment known as myohaemoglobin which differs from haemoglobin in several ways. It has a smaller molecule, and the renal threshold for this substance is much lower than for haemoglobin, explaining the reason why none of the pigment is seen in the blood-stream in these cases.

Bywaters, Delory, Rimington and Smiles[22] identified the pigment in the urine of cases exhibiting the compression syndrome as being identical with myohaemoglobin extracted from traumatized and

perfused human muscle. The significance of this lay, not so much in the fact that myohaemoglobin might be the cause of the renal failure, but in that it definitely incriminated muscle damage in this connexion.

It would appear, in the light of present knowledge, that the association between compression of muscle tissue and subsequent renal failure is based on the following possibilities:

(1) That the urinary failure follows tubular obstruction due to the formation of pigmented casts, the pigment being myohaemoglobin liberated from compressed muscle fibres, rapidly excreted owing to the small size of its molecule and precipitated in the renal tubules in the presence of a concentrated, acid urine. Evidence of the correctness of this conception would lie in the prevention of renal failure in these circumstances by maintaining an alkaline urine.

(2) That, at least, a contributory factor to the renal failure may be found in the high serum potassium level which may well exert toxic damaging effects on renal tubular epithelium.

In how far do these pathological and biochemical *data* apply in cases of renal failure following maternal birth trauma, and what is the *rôle* of retroplacental haemorrhage in producing renal sequelae?

The possibility of damage to the muscular structures of the pelvic floor being a source of myohaemoglobin is unconvincing, for the characteristic lesion in this area is a laceration and overstretching rather than a compression of muscle fibres. However, should the foetal head remain impacted for any length of time at the brim of the pelvis, compression of the soft muscular tissues of the birth canal between the foetal skull and bony pelvis could certainly occur.

On the other hand, the amount of muscle tissue subjected to compression would be small and, except in tonic contraction of the uterus, the compressing force would be intermittent rather than continuous. However, this fact might favour the production of renal sequelae by allowing early access to the blood-stream of potassium and myohaemoglobin.

Estimation of serum potassium levels, examination of the urine for myohaemaglobin and, if death occurs, careful histological examination of the kidneys should be carried out in those obstetric cases which exhibit signs of progressive renal failure after a prolonged and difficult labour. Therapy might well be directed towards alkalinizing the urine.

The evidence relating to the other obstetrical condition which may be followed by renal failure, namely concealed (retroplacental) haemorrhage, is complicated by the pre-eclamptic or eclamptic phenomena which so frequently accompany it, and it is significant that blood pigment casts and tubular degeneration with haemoglobinuria have been described in fatal cases of eclampsia.

Nevertheless, there is reason to believe that the concomitant toxaemia is not necessarily the cause of the renal failure in the accidental haemorrhage syndrome.

Bywaters and Belsey in a later publication[23] quote cases in which renal failure developed following severe ischaemia of muscle not due to direct compression but resulting from prolonged arterial spasm or rupture of a main artery, a state of affairs, surely, comparable with the massive ischaemic lesion found in severe cases of retroplacental haemorrhage with involvement of the myometrium.

Bratton[24] found renal lesions resembling those of the crush syndrome in 6 fatal cases of antepartum haemorrhage with anuria or oliguria, none of the patients had been given a blood transfusion. Young[17] gave details of 3 more fatal cases all with a history of accidental haemorrhage followed in 2 cases

by progressive renal failure and death in uraemic coma on the 9th and 10th days. (One patient died on the 1st day, presumably from shock and blood loss.)

A report from Professor Dible on the histological appearance of the kidney is quoted. Referring to Case 2, he states: "The picture is practically indistinguishable from that found in the kidney in cases of the crush syndrome," and, of Case 3, he reports: "The picture is essentially similar to that found in the kidney in the fatal anuria of the crush syndrome."

Referring again[17] to the matter of an aetiological relation between the retroplacental haemorrhage and the subsequent renal failure, evidence can readily be adduced to show that renal failure does not follow other types of obstetrical haemorrhage, viz. postpartum haemorrhage and haemorrhage due to placenta praevia.

Admittedly, shock is more marked in concealed accidental haemorrhage, but the time of onset of renal failure in those cases studied precluded the possibility of shock being responsible for the renal sequelae.

The frequent association of pre-eclampsia and eclampsia with accidental haemorrhage certainly tends to incriminate the toxaemia as a possible cause of the anuria. But renal failure is by no means a constant feature in eclampsia, and in at least one of the reported cases a fatal anuria followed an accidental haemorrhage to which trauma rather than toxaemia appeared to have contributed. On the other hand, it must be admitted that, in spite of the close analogy between uteroplacental apoplexia and other types of massive muscle ischaemia, the former lesion may be present in a marked degree without subsequent renal failure.

Thus the available evidence is obviously incomplete but the subject merits further investigation. That premature conclusions should not be drawn as to cause and effect in the accidental haemorrhage—renal failure syndrome is perhaps shown by the following case report. It tells of a woman who died from renal failure on the 9th day following a concealed accidental haemorrhage, but in whom the renal failure could not be accepted (for reasons shown at autopsy) as the result of the haemorrhage.

CASE 6.

Mrs. H. J. was a primipara, aged 28 years, who was delivered, at term, of a stillborn macerated foetus at 3.15 a.m. on March 6th, 1944, following an accidental (retroplacental) haemorrhage. She had been receiving treatment privately, over a short period, for raised blood-pressure. There was no appreciable degree of shock at the time of confinement but 21 hours later (i.e. up till midnight on March 6th) only 165 c.c. of urine had been secreted.

On March 7th, the 24 hours' urinary output was only 60 c.c. and, on March 8th, it was 75 c.c. The blood-pressure was 150/95 mm. Hg. and a deposit of albumin was present in the urine. The patient was drowsy and there was frequent vomiting of brownish fluid.

On March 9th, however, 300 c.c. of urine were secreted, followed by 750 c.c. on March 10th; vomiting had ceased but the patient was oedematous and semi-comatose. Subsequently, there was little change in the clinical picture; the urinary output was 690 c.c. on March 11th, 630 c.c. on March 12th, 1,815 c.c. on March 13th, and 2,040 c.c. on March 14th; but, in spite of the relative diuresis death occurred at 9.0 a.m. on March 13th.

At autopsy, the kidneys were found to be pale and oedematous; histologically there was some diffuse cast formation but these did not resemble myohaemoglobin casts. The general histological appearance of the kidney was that of an "arteriosclerotic nephrosclerosis with shrinkage and hyaline obliteration of many glomerular tufts, focal interstitial fibrosis, and capillary dilatation of remaining tufts."

SYMMETRICAL CORTICAL NECROSIS OF THE KIDNEYS.

Renal failure is the prominent and characteristic feature of this condition which is not peculiar to pregnancy but, nevertheless,

is most frequently associated therewith, especially when the pregnancy has been complicated by a pre-eclamptic or eclamptic toxaemia.

A coincident accidental haemorrhage has been noted in a significant proportion of cases. Although alternative theories have been put forward, there is reason to believe that the condition is due to spasm of the terminal arterioles of the kidney with resultant thrombosis and ischaemic necrosis leading to the production of a typical zone of necrotic cortex varying in depth, but forming a complete covering around the kidney. Evidence of stasis is present in the arterioles supplying the renal cortex.

Clinically, the condition is characterized by an extreme oliguria passing on to an anuria, a transient haematuria in the early stages, and a gradually progressive uraemia which often kills the patient in from 6 to 14 days, the clinical picture thus resembling, in many ways, that of a surgical anuria.

In spite of the rarity of the disease and the impossibility of establishing a definite diagnosis without biopsy or autopsy, the development of the clinical syndrome described in a patient suffering from a severe pregnancy toxaemia, especially if complicated by an accidental haemorrhage, would justify a provisional diagnosis of symmetrical cortical necrosis of the kidneys.

The question naturally arises as to whether any special aetiological significance may be attached to the frequently associated accidental haemorrhage in view of the evidence that the latter condition may, *per se*, be a cause of subsequent renal failure. The kidney pathology, both gross and histological however, presents such striking differences in the two conditions that a common aetiology would seem unlikely.

The accidental haemorrhage rate is likely to be high in any series of severe toxaemias (such as usually precede cortical necrosis of the kidneys), and it is probable that the more common retroplacental haemorrhage and the occasional case of symmetrical cortical necrosis are both manifestations of the toxic damage to vascular endothelium and the general vasomotor irritability so characteristic of the pregnancy toxaemias.

A point of practical importance is whether there is a stage in the sequence of events leading up to the condition of cortical renal necrosis, as seen in the autopsy room, when the restoration of normal vasomotor tone might lead to the recovery of renal function before the formation of secondary thrombi had produced the ischaemic necrosis.

The experimental work of Ricker[25] that terminal vascular segments of a tissue respond to weak irritation by vasodilatation and hyperaemia, to medium irritation by vasoconstriction and ischaemia, and to strong irritation by proximal vasoconstriction and peripheral vasoparalysis (with resultant thrombosis), suggests that the formation of actual thrombi may represent a comparatively late stage in a process initiated by the pregnancy toxaemia which, I feel, may be regarded, in these cases, as the source of the irritant just as chemical irritants (ethylene glycoll) have been incriminated in other reported instances of cortical necrosis unassociated with pregnancy.[2]

Actually, of course, the majority of cases do occur as a complication of pregnancy toxaemias, and the reason may lie in the consequent presence of additional factors predisposing to intrarenal thrombosis, viz. a general (and intrarenal) vasomotor instability producing a ready response to circulating irritants, toxic damage to vascular endothelium and, possibly, an increased coagulability of the blood, all tending to favour the formation of thrombi.

It seems worth attempting to correlate Ricker's conception of the 3 stages in the pathogenesis of cortical necrosis with the clinical course of the disease, thus:

Stage 1. Renal (cortical) hyperaemia due to vasodilatation with increased blood supply within the kidney but a reduced blood-flow through the glomeruli. The latter condition would explain the initial oliguria, and the former the transient haematuria.

Stage 2. Renal (cortical) ischaemia due to vasoconstriction. Clinically, this would be manifested by a more severe degree of urinary suppression, often amounting to an anuria, the disappearance of blood from the urine and a rise in the blood-nitrogen level.

Stage 3. Renal (cortical) necrosis of ischaemic origin following the formation of thrombi as described. This would be characterized, clinically, by an almost complete anuria leading to azotaemia, terminal uraemic manifestations (these may be absent in some cases) and death towards the end of the 2nd week.

If such correlation between the clinical and pathological *data* be accepted, it is clear that the possibilities of recovery may exist during the 1st and 2nd stages of the development of complete cortical necrosis. The irreversible changes characteristic of the 3rd stage could, perhaps, be prevented if, during the 2nd stage:

(*a*) the arteriolar vasoconstriction could be relieved, if only temporarily, in the first instance; and

(*b*) some diuretic substance could increase the excretory capacity of such cortical tissue as may thus have been relieved of its ischaemic condition.

The case report to be quoted suggests, even admitting the possibility of spontaneous recovery, that the repeated intravenous administration of hypertonic glucose solutions may act in such a way.

Dieckmann,[2] discussing the treatment of the oliguria of eclampsia by this method, expresses the opinion that the rapidity of the diuresis effected by parenteral hypertonic glucose, indicates that the urinary suppression is due to arteriolar spasm rather than to oedema of the kidney. Examination of the capillaries of the nail bed during such treatment revealed definite improvement in the circulation, including the disappearance of beading in some cases.

That such relief of vasoconstriction may, initially, be only transient unless the treatment were repeated, would not necessarily detract from its value in cortical necrosis for the diuresis, which in a favourable case would follow, may so effectively rid the blood-stream of irritant toxins that the stimulus to a return of the vasospastic state would be lacking. (To what extent is the fall in blood-pressure of the post-eclamptic patient the result of the diuresis which so often accompanies recovery?) Moreover, there are no great technical difficulties in repeating the treatment if careful selection of veins is exercised. The clinical details of the case referred to are as follows:

CASE 7.

Mrs. V. T. was a primipara, aged 22 years, who, prior to her confinement on September 6th, 1942, had been treated for pre-eclamptic toxaemia. There had not been any accidental haemorrhage. Just before the delivery 75 c.c. of urine had been withdrawn from the bladder by catheterization but there was no further urinary secretion during the day (the confinement having taken place at 7.0 a.m.). The patient was admitted to hospital at this stage.

On September 7th there was complete anuria but the patient looked well and stated that she felt well. There was no oedema.

On September 8th 45 c.c. of blood-stained urine were obtained by catheterization, making a total of 120 c.c. of urine secreted in 3 days.

The blood urea was estimated to be 196 mg. per 100 c.c. of blood. Only a cloud of albumin was present in the urine. The patient was inclined to be drowsy but otherwise seemed well; 500 c.c. of 25 per cent glucose solution were given intravenously.

On September 9th 390 c.c. of urine were secreted. Albumin or blood were not present and microscopic examination failed to reveal any casts.

The blood urea was 208 mg. per 100 c.c. of blood and the general condition of the patient was unchanged. The blood-pressure readings, which had previously shown considerable fluctuation, were now consistently within normal limits (120 mm. Hg.). A further 1,200 c.c. of 25 per cent glucose solution were given intravenously.

On September 10th 900 c.c. of urine were secreted and, during the next 4 days, the 24 hours' output measured 1,560 c.c., 2,040 c.c., 1,890 c.c., and 2,520 c.c. respectively, and continued at a satisfactory figure thereafter.

Nevertheless, the blood urea was till 260 mg. per 100 c.c. of blood on the 7th day after admission, 147 mg. per 100 c.c. on the 12th day, and 65 mg. per 100 c.c. on the 21st day.

Clinically, the improvement in the condition of the patient herself began on the 4th day after admission and continued steadily thereafter, preceding at all stages the fall in the blood urea estimations.

Summary.

1. The subject of renal failure from the point of view of the obstetrician is introduced by a recapitulation of some relevant facts of renal physiology.

2. The pharmacology of various diuretic substances is discussed.

3. The pathogenesis, clinical features, lines of investigation and methods of treatment of renal failure as encountered in obstetric practice are considered with especial reference to eclampsia, acute glomerulonephritis, renal failure occurring as a sequel to transfusion accidents involving the Rh factor, as a sequel to concealed accidental haemorrhage or following a prolonged and difficult labour.

4. Symmetrical cortical necrosis of the kidneys is also considered in some detail, and certain suggestions are made linking pathogenesis, clinical manifestations and treatment.

5. Typical case records are quoted illustrating each of these different clinicopathological types of renal failure.

Conclusions.

It is obvious that there are still many gaps in our knowledge of the factors involved in the development of renal failure complicating obstetrical conditions.

Therapy, however, is becoming more rational as evidence accumulates of the underlying pathology and biochemistry of the various clinical types of renal failure.

Further development may be expected in this field of investigation.

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The Definition of Prematurity

A Proposed Minimal Weight Standard for Viable Premature Infants.

BY

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IT is unfortunate that a minimal weight standard for viable premature infants was not adopted concurrently with the maximal weight standard of $5\frac{1}{2}$ pounds ($2\frac{1}{2}$ kilograms). The weight range of viable premature infants would thus have been exactly defined and a scientific basis provided for statistics relating to them. McNeil,[1] in a Finlayson Memorial Lecture, drew attention to the desirability of adopting a minimal weight standard of viability, and pointed out that the absence of a universal minimal standard makes the comparison of figures relating to the frequency and mortality of premature infants almost valueless. The rectification of this omission is overdue and a minimal weight standard is proposed in this paper. The suggested standard has been formulated by comparing the estimated period of gestation with the birth-weight in a large number of premature infants, and finding the average weight of infants with an estimated gestation period of 28 weeks—the age at which the foetus is generally presumed to become viable.

A weight standard of viability of 1,000 g. (2 pounds, 3.2 ounces) has been adopted by some workers, particularly in the United States, while others regard infants of less than 1,500 g. (3 pounds, 4.8 ounces) as non-viable. Various weight standards between these two extremes are also in use.

The Maximal Weight Standard of $5\frac{1}{2}$ Pounds.

This upper-weight standard of prematurity, which was not officially adopted in the English-speaking countries until the later year of 1930, has been advocated and used by various authorities for many years. Ylppö,[2] in his classical treatise on prematurity, defined as premature those infants with a birth-weight under 2,500 g.: he advocated, on both clinical and statistical grounds, the universal adoption of this standard as the most desirable arbitrary dividing-line between mature and premature infants. Ylppö's work had great influence on the European Continent, where the standard of 2,500 g. or less soon became general. This standard was also used by numerous workers in the United States prior to its official adoption by the American Academy of Pediatrics in 1935. The Academy defined prematurity in the following terms: "For statistical purposes and comparison of results of care, a uniform standard for diagnosis of prematurity is important. A premature infant is one who weighs 2,500 g. or less at birth (not on admission) regardless of the period of gestation. All liveborn premature infants should be included, evidence of life being heart-beating or breathing."[3]

In Great Britain an incomplete period of gestation continued to be the criterion of prematurity until 1938, when a joint

committee of the Royal College of Physicians of London and the Royal College of Obstetricians and Gynaecologists was appointed to recommend a more suitable definition of prematurity. The committee adopted the following standard: "That in conformity with the standard in international use an infant whose birth-weight is $5\frac{1}{2}$ pounds (approximately 2,500 g.) or less should be considered, for the purpose of comparison of records, as either immature or prematurely born, according as the estimated period of gestation is full-time or less."[4] The reservations in the latter part of this definition bear the imprint of compromise and seem unnecessarily to impair its clarity; they have been ignored in practice and the more precise American standard, which states that "a premature infant is one who weighs 2,500 g. or less at birth regardless of the period of gestation," has been generally adopted in this country.

The introduction of this maximal weight standard of prematurity has proved to be of great value for statistical purposes. Both obstetricians and paediatricians have found it much more satisfactory than an estimated incomplete period of gestation, which had always been the criterion of prematurity up to that time. The principal drawbacks of the old definition are (*a*) The frequent uncertainty regarding the date of onset of the last menstrual period; (*b*) The frequency with which infants judged to be premature weigh 6 to 7 pounds or more; (*c*) The frequency with which infants judged to be mature weigh $5\frac{1}{2}$ pounds or less. The weight of $5\frac{1}{2}$ pounds (2,500 g.) is the most suitable arbitrary dividing-line between mature and premature infants for two main reasons: (*a*) Because infants below this weight require special nursing care and special feeding methods. (*b*) Because $5\frac{1}{2}$ pounds corresponds exactly with $2\frac{1}{2}$ kg., an essential correspondence between the avoirdupois and metric systems which cannot be obtained in round figures at any other point in the neighbourhood of 5 to 6 pounds.

Relation of Birth-Weight and Estimated Period of Gestation in 1,041 *Liveborn Premature Infants* (*Twins Excluded*).

This is shown in tabular form (Table I) and graphically (Fig. 1). Twin infants totalling 252 have been excluded because the average period of gestation is greater in twin infants than in single infants of a corresponding weight. This fact necessitates their exclusion in determining the normal relation between the birth-weight and the period of gestation, because the proportion of twin infants differs in each weight group. Stillborn and deadborn premature infants have also been excluded from this calculation because, in their case, the relation of the weight and the foetal age is very variable owing to the frequency of

TABLE I.

Relation of Birth-weight and Estimated Period of Gestation in 1,041 *Liveborn Premature Infants* (*Twins Excluded*).

	Weight in pounds							
	5½ to 5	5 to 4½	4½ to 4	4 to 3½	3½ to 3	3 to 2½	2½ to 2	2 to 1½
No. of infants ...	423	207	146	90	75	44	34	22
Period of gestation ... (average in weeks)	37.6	35.9	35.0	33.0	31.6	28.9	27.7	26.4

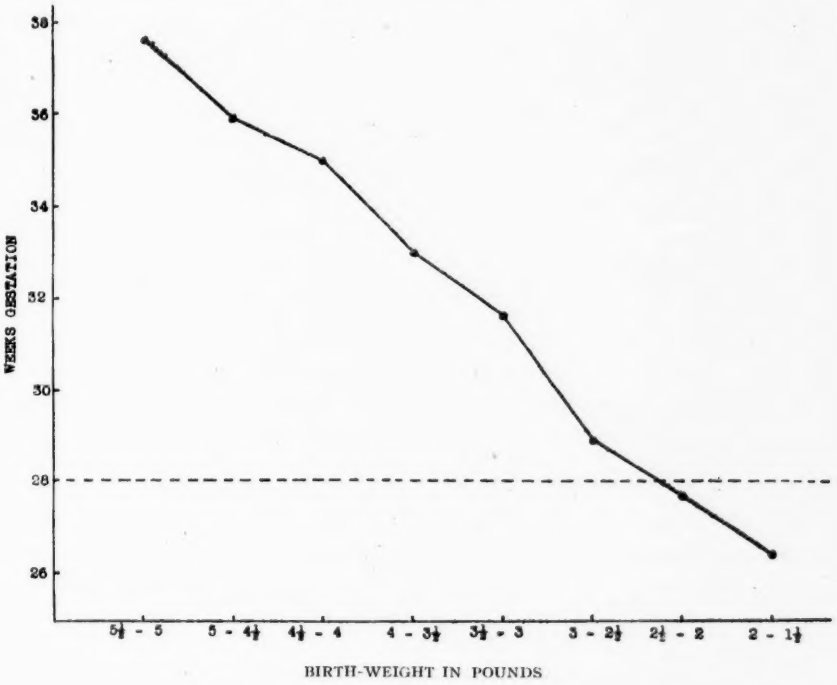

FIG. 1.

Relation of birth-weight and estimated period of gestation in 1,041 liveborn premature infants (twins excluded).

gross congenital defects and intra-uterine death. It will be observed that the 44 infants in the 3 to 2½ pounds weight group averaged 28.9 weeks gestation and the 34 infants in the 2½ to 2 pounds group averaged 27.7 weeks gestation. The lower-weight limit of viability would appear, therefore, to lie between 3 pounds and 2 pounds. There is an important reason why the average weight of infants of 28 weeks gestation cannot be accurately calculated from hospital records. It is dependent on the general practice of regarding many infants who have a gestation period of 26 to 28 weeks as viable, and recording them as being over 28 weeks gestation so that the mother will receive her maternity benefit. Such a practice would seem quite justifiable, for the duration of gestation is only an approximate estimation and it is certainly right that the mother should receive the benefit of any doubt in borderline cases. From the statistical point of view, however, this practice vitiates the figures relating to the lower weight groups of premature infants, as a considerable number of previable infants are notified as viable. The conclusion must be drawn, therefore, that the figure of 28.9 weeks exceeds the actual period of gestation in the 3 to 2½ pounds group and that the average weight of infants of 28 weeks gestation probably lies somewhere between 3 and 2½ pounds.

The Proposed Minimal Weight Standard.

The weight of 2¾ pounds (2 pounds, 12 ounces), which corresponds exactly with 1¼ kg. (1,250 g.), would appear, in view

of the evidence presented in this paper, to be the most desirable minimal arbitrary weight standard for premature infants.

The reasons for selecting this figure are as follows:

(1) The average weight of infants of 28 weeks gestation appears to lie between 3 and $2\frac{1}{2}$ pounds.

(2) The weight of $2\frac{3}{4}$ pounds avoirdupois corresponds exactly with the weight of $1\frac{1}{4}$ kg. (1,250 g.) in the metric system—a correspondence in relatively round figures which cannot be obtained at any other point in the neighbourhood of 3 to $2\frac{1}{2}$ pounds.

(3) The minimal figures of $2\frac{3}{4}$ pounds and $1\frac{1}{4}$ kg. are exactly half the maximal figures of $5\frac{1}{2}$ pounds and $2\frac{1}{2}$ kg. respectively, a fact which makes them easy to remember as the maximal figures are now in general use.

years period 1938 to 1943—an incidence of 7.9 pre-viable liveborn infants per 1,000 live-births. The total number of mature, premature and pre-viable liveborn infants in the 6-years period is given in Table II, also the incidence in each group.

Survival of Pre-viable Infants. Only 4 of the 118 pre-viable infants survived—a death-rate of 966 per 1,000. Three of these survivors were twins, who have a better chance of survival than single infants of a corresponding weight. This is a very low survival-rate but various authorities[5, 6, 7] have demonstrated that much better figures are attainable. Nevertheless, even in the most ideal circumstances, the death-rate in infants with a birth-weight of less than 2 pounds, 12 ounces will always be very high. A comparison of the death-rate in

TABLE II.

The Incidence of Mature, Premature and Pre-viable Livebirths in a Total of 14,923 *Livebirths at the Simpson Memorial Maternity Pavilion, Royal Infirmary, Edinburgh, in the* 6*-Years Period,* 1938 *to* 1943.

	Infant Category.		
	Mature Over $5\frac{1}{2}$ pounds	Premature $5\frac{1}{2}$ to $2\frac{3}{4}$ pounds inclusive	Pre-viable Under $2\frac{3}{4}$ pounds
Number of infants ...	13,519	1,286	118
Incidence per 1,000 ...	905.9	86.2	7.9

Liveborn Pre-viable Infants (under $2\frac{3}{4}$ pounds weight). The adoption of the proposed arbitrary minimal weight standard of $2\frac{3}{4}$ pounds would necessitate the provision of a separate category for liveborn infants weighing under $2\frac{3}{4}$ pounds. The term pre-viable, which is sometimes used in the case of very small premature infants, would suitably describe this category.

A total of 118 pre-viable (under $2\frac{3}{4}$ pounds) liveborn infants were born in the Simpson Memorial Maternity Pavilion, Royal Infirmary, Edinburgh, in the six-

each $\frac{1}{2}$ pound weight group between 4 pounds and 2 pounds shows a steep rise in the 3 to $2\frac{1}{2}$ pounds group, the one which is bisected by the proposed minimal weight standard of $2\frac{3}{4}$ pounds (Table III, Fig. 2). Subdivision of this group into a viable half (3 to $2\frac{3}{4}$ pounds) and into a pre-viable half ($2\frac{3}{4}$ to $2\frac{1}{2}$ pounds) shows (Table IV) that the chances of survival are much poorer in the pre-viable half, a fact which emphasizes the appropriateness of the proposed $2\frac{3}{4}$ pounds minimal weight standard for viable premature infants.

TABLE III.

The Number of Infants and the Death-rate in each Half-pound Weight Group Between 4 pounds and 2 pounds.

	Weight group			
	4 to 3½ pounds	3½ to 3 pounds	3 to 2½ pounds	2½ to 2 pounds
Number of infants	139	98	68	58
Number of surviving infants	75	36	8	1
Death-rate per 1,000	460.4	632.7	882.4	982.8

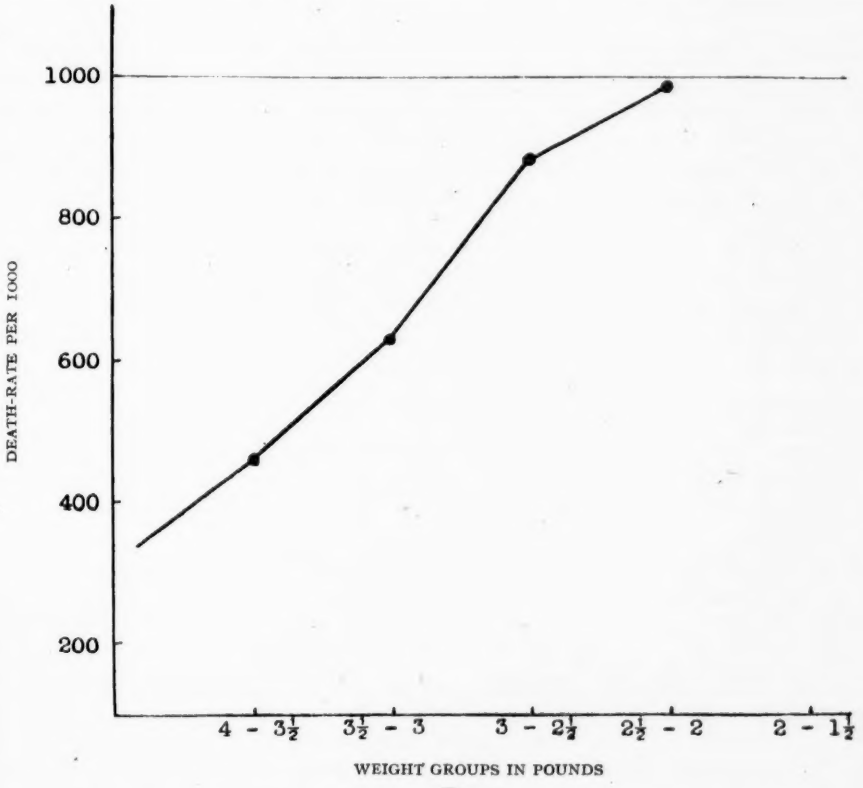

FIG. 2.

The death-rate in each half pound weight group between 4 pounds and 2 pounds.

Effect of the 2¾ pounds Minimal Standard on the Classification of Stillbirths.

The substitution of the arbitrary weight standard of 2¾ pounds for the time-honoured standard of an estimated gestation period of 28 weeks would reduce considerably the proportion of premature stillborn foetuses falling into the category of viable stillborn infants, and increase correspondingly the proportion falling into the cate-

TABLE IV.

The Number of Infants and the Death-rate in the Viable half (3 to 2¾ pounds) and in the Pre-viable half (2¾ to 2½ pounds) of the 3 to 2½ pounds Weight Group.

	Weight group	
	3 to 2¾ pounds (Viable)	2¾ to 2½ pounds (Pre-viable)
Number of infants	40	28
Number of surviving infants	6	2
Death-rate per 1,000	850.0	928.6

gory of pre-viable stillborn foetuses which are commonly termed miscarriages. The effect of this change of definition in the 6-years period at the Simpson Maternity Pavilion, referred to above, is shown in Table V. This table shows that 139 (27 per cent) foetuses classified as premature stillbirths by the 5½ pound-28 weeks standard (the current definition of prematurity) would be classified as miscarriages by the 5½ pound-2¾ pound standard (the proposed new definition of prematurity). This figure of 27 per cent is much higher than the figure of 8.4 per cent which is the proportion of liveborn infants transferred to the pre-viable category by the substitution of the proposed new definition for the current definition. The great difference in the proportion of liveborn and stillborn infants who would be classified as pre-viable instead of viable, according to the proposed minimal weight standard of 2¾ pounds, is in accordance with the universally acknowledged fact that the average weight of stillborn infants is considerably less than the average weight of liveborn infants at a corresponding period of gestation. The principal causes of the lower average weight of stillborn infants at a corresponding period of gestation are the common occurrence of gross congenital malformations such as anencephaly and of intrauterine death occurring some weeks before birth.

TABLE V.

The Effect of the 2¾ pounds Minimal Standard on the Classification of 1,108 Infants Classified as Stillbirths at the Simpson Maternity Pavilion, Royal Infirmary, Edinburgh, in the 6-years Period, 1938 to 1943.

	Mature	Premature 5½ to 2¾ pounds inclusive	Pre-viable (Miscarriage) Under 2¾ pounds
Number of infants	588	381	139
Incidence per 1,000	530.6	343.9	125.5

The considerable reduction in the number of stillbirths which would follow the adoption of the 2¾ pounds standard would appear to be desirable, because a large proportion of the foetuses which would fall into the pre-viable (miscarriage) group would show either gross congenital malformations or maceration following intrauterine death. Forty (29 per cent) of the 139 foetuses which would be classified as

miscarriages by the $2\frac{3}{4}$ pounds standard, instead of stillbirths by the current standard, showed gross congenital malformations; anencephaly accounted for 32. Accurate figures relating to intra-uterine death cannot be given but at least 20 per cent would probably fall into this category. Thirty-nine (28 per cent) of the 139 foetuses affected by the change of standard weighed less than 2 pounds at birth.

Summary.

The desirability of adopting, for statistical purposes, an arbitrary minimal weight standard for viable premature infants has been discussed.

Minimal weight standards in use vary between 1,000 g. and 1,500 g.

The evolution of the international maximal standard of $5\frac{1}{2}$ pounds or less has been traced. It apparently originated on the European Continent.

The relation of the birth-weight and the estimated period of gestation in 1,041 liveborn premature infants (twins excluded) has been investigated. The average weight of infants of 28 weeks gestation appears to be between 3 and $2\frac{1}{2}$ pounds.

A minimal arbitrary weight standard for premature infants of 2 pounds 12 ounces (1,250 g.) has been proposed for the following reasons: (a) The average weight of infants of 28 weeks gestation appears to be about $2\frac{3}{4}$ pounds. (b) The weight of $2\frac{3}{4}$ pounds avoirdupois corresponds to the weight of $1\frac{1}{4}$ kg. (1,250 g.) in the metric system. This correspondence in round figures is an essential condition of an international standard. (c) The minimal weight of $2\frac{3}{4}$ pounds is exactly half of the maximal weight of $5\frac{1}{2}$ pounds, a fact which simplifies the definition of the weight range of prematurity.

The term "pre-viable" has been proposed for the separate category of liveborn premature infants with a birth-weight of less than $2\frac{3}{4}$ pounds.

A total of 118 pre-viable infants were born in a 6-years period at the Simpson Maternity Hospital—an incidence of 7.9 per 1,000 live-births. Only 4 survived—a death-rate of 966 per 1,000. Better figures are attainable, but the mortality of infants weighing less than $2\frac{3}{4}$ pounds at birth will always be very high.

The effect of the $2\frac{3}{4}$ pounds minimal standard on the classification of stillbirths has been discussed. In the 6-years period reviewed 27 per cent (139) of the premature foetuses classified as stillbirths ($5\frac{1}{2}$ pounds —28 weeks' gestation standard) weighed less than $2\frac{3}{4}$ pounds and would be classified as pre-viable (miscarriages) according to the proposed new definition.

A much larger proportion of stillborn infants of $5\frac{1}{2}$ pounds or less (27 per cent) than of liveborn infants of $5\frac{1}{2}$ pounds or less (8.4 per cent) would be excluded from the category of viable premature infants by the lower limit of $2\frac{3}{4}$ pounds than by the current lower limit of an estimated gestation period of 28 weeks. This would seem desirable as about half of the excluded stillborn foetuses in the period under review were cases of gross congenital malformation or of maceration following intra-uterine death.

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The Value of the Rhesus Test in Obstetrics

BY

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IN 1940, Landsteiner and Wiener[1] demonstrated the presence of the Rh factor in the red cells of 85 per cent of human beings. Following this, Wiener and Peters,[2] and Wiener[3, 4] showed that certain individuals, whose red cells lacked this factor (Rh negative), were capable of producing an Rh antibody which would agglutinate the red cells of Rh positive persons. This production of Rh antibody could result from stimulation by either a previous transfusion with Rh positive blood or, in the case of women, by bearing an Rh positive child. Following this, Levine, Katzin and Burnham[5] suggested that erythroblastosis foetalis, or as it is better called "haemolytic disease of the newborn," was due to the haemolysis of the infant's red cells by Rh antibody. According to their hypothesis, an Rh negative woman with an Rh positive husband and carrying an Rh positive foetus might become immunized by her infant's red cells and produce an Rh antibody which passed back through the placenta and caused haemolysis of the infant's red cells. This hypothesis has been amply confirmed by subsequent workers (Boorman, Dodd and Mollison,[6] Race, Taylor, Cappell and McFarlane.[7] Boorman, Dodd and Mollison,[8] Kariher and Spindler,[9] Potter, Davidsohn and Crunden[10]). Further recent work has shown that there are at least 7 Rh genes (Race, Taylor, Cappell and McFarlane[11]) with 28 possible genotypes, and that in order to produce Rh antibody, a mother need not necessarily be Rh negative (McCall, Race and Taylor[12]). Taylor and Race[13] have also shown that the likelihood of a child suffering from erythroblastosis foetalis is considerably greater if the father is a homzygous Rh positive (genotype Rh Rh) than if he is heterozygous (genotype Rh rh).

Boorman and Dodd[14] have shown that the Rh factor is present not only in the red cells but also in body fluids and in the cells of a number of tissues. This finding raises the possibility that Rh antibody might react with tissue cells and produce other effects than those of recognizable haemolytic disease. In this connexion it is interesting to note that Javert[15] has found evidence of congenital abnormalities in 22 per cent of his cases of haemolytic disease of the newborn, though it should be noted that they were practically all instances of very minor abnormalities. Apart from this there is the possibility of other effects being produced in both mother and foetus by Rh antibodies, as for example repeated stillbirths, repeated abortions and possibly even toxaemias of pregnancy, since Javert[15] has noted an association between eclampsia and hydrops foetalis.

During the past 18 months we have investigated the Rh reactions of 280 selected obstetrical cases. These were sent to us by our clinical colleagues either because they considered that the infants were suffering from haemolytic disease of the newborn or because they suspected that the Rh factor might be the cause of other obstetric mis-

haps of the types mentioned above. In brief, our results have confirmed those of other workers with regard to haemolytic disease of the newborn and we put forward evidence to support the existence of a 4th variant of this disease. We have failed to show a connexion between the Rh factor and any other condition and we publish these negative results in the hope of saving unnecessary investigations.

Technique. Whenever possible we have obtained sterile samples of whole, coagulated blood. From this, both cells and serum can be obtained and we have found that the red cells are better preserved this way especially when there is any delay, as in posted specimens. If possible we have left the whole specimen in the refrigerator at 2–4°C. over night and decanted the serum cold next morning in order to get rid of any possible cold agglutinins. The test has been done according to the technique of Boorman, Dodd and Mollison.[6] At the beginning, before the various Rh genotypes were recognized, we relied on using several Rh antisera to detect Rh positive red blood cells. Later we were able to use sera containing known Rh antibodies (ρ, ρ_1, and ρ_2). This is necessary because Rh positive red blood cells of certain genotypes do not agglutinate with the common Rh antibody (ρ), and, if this antibody alone is used, will be wrongly diagnosed as Rh negative. The serum was tested for antibody in all cases irrespective of the Rh group of the cells because it has been shown that Rh antibody may occur in an Rh positive individual (McCall, Race and Taylor[12]) and we have in fact encountered 5 such cases, 3 of them in this series. In testing for the presence of Rh antibody in the patient's serum it is necessary to use a series of Rh positive red blood cells of known genotype, otherwise certain of the rarer Rh antibodies (ρ_1, or ρ_2) may be missed. It is also necessary to test the unknown serum against known Rh negative cells firstly as a control and secondly because both Levine, Javert and Katzin[16] and McCall, Race and Taylor[12] have discovered sera which agglutinate such cells.

Results. Our findings in this series of 280 cases are summarized in Table I.

TABLE I.
Distribution of Rh Groups Among 280 Cases.

	No.	With Rh antibody	Without Rh antibody
Rh +	196	3	193
Rh −	84	58	26
Totals	280	61	219

Of the whole series 196 were Rh positive and 84 Rh negative. Rh antibody was demonstrated in 61 cases (Table II). Of these 53 were clinically recognizable examples of haemolytic disease of the newborn; the remaining 8 cases were atypical and will be discussed in detail later.

TABLE II.
Distribution of Cases with Demonstrable Rh Antibody.

Form of haemolytic disease of the newborn	Rh−	Rh+	Total
Hydrops foetalis	8	0	8
Icterus gravis	27	0	27
Haemolytic anaemia	16	2	18
Other cases	7	1	8

In this series we have not encountered any examples of Rh antibody associated with a healthy baby, nor of clinical haemolytic disease of the newborn in the absence of Rh antibody though both have been observed by other workers (Boorman, Dodd and Mollison[6]), the haemolysis in the latter cases being apparently due to high titre anti A. or anti B. agglutinin.

It will be noted that in this series we encountered 3 Rh positive mothers whose sera contained Rh antibody. All 3 be-

longed to the rarer Rh positive genotypes (Rh_1Rh_1, Rh″rh, and Rh′rh) and their sera agglutinated the cells of certain Rh positive genotypes other than those to which they belonged. These cases illustrate the importance of a complete examination of both cells and sera in all cases in which Rh investigation is undertaken.

In 2 cases of hydrops we had the opportunity of testing the serum for antibody at intervals during pregnancy.

CASE 1.

Mrs. S., aged 27 years. Group O. Rh negative. 1st and 2nd children normal. 3rd child died of icterus gravis. 4th child died *in utero*. Born macerated at 38 weeks. 5th child hydrops foetalis, delivered at 33 weeks. 6th child hydrops foetalis, delivered at 29 weeks.

Blood examined during the 7th pregnancy at 17th and 20th weeks and on the 8th day after delivery of a foetus with hydrops. The results are as follows.

Rh Antibody Titre During Pregnancy in Case 1.

Time	17th week	20th week	36th week	8th day puerperium
Antibody titre	1/16	Nil	Delivered	1/512

CASE 2.

Mrs. M., aged 19 years. Group O. Rh negative. 1st baby icterus gravis, transfused with Rh negative blood and recovered. 2nd baby stillborn with hydrops.

Blood tested twice during the 1st puerperium and at intervals during the 2nd pregnancy and puerperium. The results are as follows.

The interest of these 2 cases lies in the diminution of antibody during the latter part of pregnancy. We believe that it is evidence that in cases of haemolytic disease of the newborn the antibody is absorbed and used up by the foetus and that the actual quantity used is not sufficient to alter the titre of circulating antibody until the foetus reaches a certain size, apparently some time about the 20th week. If this is true then this diminution of antibody titre has prognostic significance. The mere finding of antibody during pregnancy does not prove that the foetus will necessarily suffer from haemolytic disease of the newborn, firstly, because the antibody may be residual from a previous pregnancy and the foetus may be Rh negative and therefore not affected, and secondly, because on rare occasions it has been observed that an Rh negative mother with Rh antibody (observed during the puerperium) may have an Rh positive baby which does not show any signs of haemolytic disease of the newborn. (Boorman, Dodd and Mollison.[6]) If, as we suppose, the diminution of antibody indicates its absorption by the foetus, then it presumably indicates that the baby will show haemolytic disease of the newborn.

In Table II we draw attention to the fact that in addition to the 53 cases of classical haemolytic disease of the newborn demonstrable Rh antibody had been found in 8 other cases. In all 8 the foetus died *in utero* at or shortly before term and was usually born macerated. Certain workers

Rh antibody Titre during pregnancy in Case 2.

	1st pregnancy		2nd pregnancy							
Time	Puerperium 4th day	Puerperium 18th day	5 weeks	16 weeks	20 weeks	24 weeks	30 weeks	33 weeks	34 weeks	14th day puerperium
Antibody titre	1/64	1/512	1/512	1/512	1/32	1/32	1/32	1/32	1/32	1/1024

(Javert,[15, 17] Henderson,[18, 19]) have suggested that there is a 4th variant of haemolytic disease of the newborn which takes this form and in which although, due to maceration, an excessive erythropoiesis cannot usually be demonstrated, there are signs of damage to the liver with fibrosis. Our findings strongly support this view and we would urge that the clinical entity "haemolytic disease of the newborn" should in future be used to cover this 4th variant of its manifestations.

The histories of our 8 cases, which are summarized in Table III, were briefly as follows:

Case 1. (C.B., 28 years.)

1st child normal. Group A. Rh positive. 2nd child stillbirth (cause uncertain). 3rd child stillbirth (cause uncertain).

First tested at 8th week of 4th pregnancy. Group A. Rh negative, antibody titre 1/16. Retested 16th week of pregnancy, antibody titre 1/32. Retested 34th week of pregnancy, antibody titre 1/2. Foetal movements ceased at 36th week. Retested at 37th week, titre 1/16. Delivered at 37th week, of a macerated foetus. Retested during puerperium antibody titre 1/16.

Case 2. (R.C., 42 years.)

1st child full-time stillbirth. 2nd child normal. 3rd twins normal. 4th child normal. 5th full-time stillbirth. 6th stillbirth premature. 7th stillbirth full-time. 8th stillbirth full-time. 9th stillbirth full-time. 10th stillbirth premature. 11th stillbirth macerated. 12th pregnancy, tested at 28th week of pregnancy. Group O. Rh negative, antibody present. Unfortunately we were unable to retest the blood. Patient delivered of a macerated foetus.

Case 3. (O.B., 27 years.)

1st pregnancy delivered at 3 weeks post mature stillbirth (cause unknown). 2nd pregnancy, full-time, stillbirth (cause unknown). 3rd pregnancy, tested at 33rd week. Group A_2. Rh negative, antibody titre 1/24.

34th week foetal movements ceased. 36th week delivered of a stillborn macerated foetus. Retested 1 week later, antibody titre 1/512.

Table III.

Case	Age	Group	Antibody	Pregnancies					
				1	2	3	4	5	6
1	28	A. Rh−	+	N	SB	SB	IUD		
2	42	O. Rh−	+	(1) SB	(2) N	(3) Twins N	(4) N	(5) SB	(6) SB
				(7) SB	(8) SB	(9) SB	(10) SB	(11) IUD	(12) IUD
3	27	A_2 Rh−	+	SB	SB	IUD			
4	33	O. Rh−	+	Misc.	ND	ND	ND	IG	IUD
5	28	O. Rh−	+	N	ND	IUD			
6	?	O. Rh−	+	N	N	IUD			
7	35	O. Rh−	+	N	IG	IUD			
8	27	A. Rh+	+	N	N	IG	IUD		

N = Normal infant. SB = Stillbirth. IUD = Intrauterine death with macerated foetus.
ND = Neonatal death. IG = Icterus gravis.

Case 4. (Mrs. I., 33 years.)

1st pregnancy, miscarriage at 20th week. 2nd pregnancy, normal delivery. Neonatal death at 2nd day (cause unknown). 3rd pregnancy, labour induced at 28th week. Neonatal death (cause unknown). 4th pregnancy, labour induced at 28th week. Neonatal death (cause unknown). 5th pregnancy, labour induced at 32nd week, child showed icterus gravis but recovered (before the discovery of the Rh factor). 6th pregnancy, blood tested at 20th week. Group O. Rh negative. An antibody not demonstrated.

Retested at 30th week, antibody present in neat serum only. 36th week delivered of a macerated foetus.

CASE 5. (Mrs. R., 28 years.)

1st pregnancy, normal child. 2nd pregnancy, neonatal death (probably haemorrhagic disease of newborn). 3rd pregnancy, blood tested at 26th week, Group O. Rh negative. Antibody titre 1/128. Delivered at 36th week of a macerated foetus. Retested 6 weeks after delivery. Antibody titre 1/32.

CASE 6. (Mrs. R.)

1st pregnancy, normal child. 2nd pregnancy, normal child. 3rd pregnancy, delivered of a macerated foetus.

Blood tested at 10th day of puerperium. Group O. Rh negative, antibody titre 1/4.

CASE 7. (H.S., 35 years.)

1st pregnancy, normal child. 2nd pregnancy, child died of icterus gravis. 3rd pregnancy, intrauterine death at 29th week.

Blood tested at 19th day of puerperium. Group O. Rh negative, antibody 1/128.

CASE 8. (E.F., 27 years.)

1st pregnancy, normal child. 2nd pregnancy, normal child. (Group A. Rh positive). 3rd pregnancy child died icterus gravis. 4th pregnancy, blood tested at 33rd week. Group A_2. Rh positive genotype either Rh" rh or Rh" Rh" Rh antibody titre 1/2. Retested 36th week, antibody titre 1/4,000. Delivered 38th week of a macerated foetus. Retested 14th day of puerperium (about 18 days after death of foetus), titre 1/64.

It will be seen that in cases 4, 7 and 8 there was a history of haemolytic disease of the newborn in previous infants which, in view of the strong tendency of this disease to recur in each pregnancy, is evidence in favour of these cases being variants of haemolytic disease of the newborn. This view is also supported by a study of the antibody titres in 2 cases. In Case 1 it will be noted that the titre fell during the latter half of pregnancy and rose again after the death of the foetus, while in case 3, the titre rose after delivery.

If, as we believe, the low titre during the latter part of pregnancy indicated an absorption of antibody by the foetus, then it seems reasonable to suppose that the death of the foetus was associated with this absorption of antibody and that therefore the death was due to a form of haemolytic disease of the newborn.

Apart from these 61 cases of definite and supposed haemolytic disease of the newborn there were 10 cases of neonatal jaundice in which we were unable to demonstrate Rh antibody. In none of these cases was the clinical picture diagnostic of haemolytic disease of the newborn nor was there a significant degree of anaemia. We believe that they were cases of physiological jaundice.

In the remaining 209 cases in which Rh antibody was not demonstrable, the patients gave histories of a variety of obstetric mishaps, the 6 main ones being repeated abortions, unexplained stillbirths, unexplained neonatal deaths, congenital abnormalities, haemorrhagic disease of the newborn and toxaemias of pregnancy. It is difficult to classify these cases fully because many patients give a history of more than one condition but the number of patients giving a history of each condition was as follows:

1. Repeated abortions (up to 8 times)	112 cases
2. Unexplained stillbirths	103 cases
3. Unexplained neonatal deaths ...	47 cases
4. Congenital abnormalities	20 cases
5. Haemorrhagic disease of the newborn	4 cases
6. Toxaemias of pregnancy	16 cases

Of these 209 cases, 26 (12.4 per cent) were Rh negative and 183 (87.6 per cent) were Rh positive. These figures are in fairly close agreement with Landsteiner and Wiener's[1] figures of 15 per cent and 85 per cent respectively for the general population. In all cases the serum was tested for Rh antibody irrespective of the Rh group of the cells and in the vast majority of cases

the tests were carried out at a time when antibody, if present, could be expected to be at about its maximum.

In our series a history of repeated abortions was the commonest reason for asking for an Rh investigation; the supposition being that if Rh antibody can cause death of the foetus at or near term it may also cause miscarriage at an earlier stage. In fact our evidence is all to the contrary. In no single instance did we find any Rh antibody present and we feel that a series of over 100 cases is sufficient to give this result reasonable significance. Furthermore, if there were any connexion between the Rh factor and repeated abortions one would expect to find a history of the latter in the true cases of haemolytic disease of the newborn: in fact among our 61 cases, 6 only had a history of one abortion each.

Unexplained stillbirths was the other common reason for asking for an Rh investigation. Here the problem of deciding whether such an investigation would be of value is more difficult. Haemolytic disease of the newborn can cause stillbirths by hydrops or, as we have shown, by causing intrauterine death of the foetus. In these cases the investigation will almost certainly show the presence of Rh antibody and confirm the diagnosis and in the latter type of case is likely to be especially helpful in forming a prognosis. Apart from these 2 types of case however we have found no evidence of any connexion between the Rh factor and stillbirths.

Forty-seven of our cases gave a history of unexplained neonatal deaths. These were cases in which death could not be attributed to either icterus gravis or haemolytic anaemia on clinical grounds but in which it was thought possible that the Rh factor might have been responsible in some other way. In none of these patients were we able to find any evidence of Rh antibody.

In the group of congenital abnormalities we had 20 patients, 5 of whom had given birth to 2 affected infants, that is 25 abnormal infants in all. The lesions were as follows:

Anencephaly	12 cases
Spinabifida	6 cases
Hydrocephalus	2 cases
Imperforate anus	1 case
Cleft palate and harelip	1 case
Hare lip	1 case
Atresia of the duodenum	1 case
Unknown	1 case
	25 cases

It will be seen that the lesions are nearly all major ones and it seems reasonable to assume that if the Rh factor were responsible, we should have encountered Rh antibody in at least some of the cases or that we should have found a high percentage of Rh negative mothers. Actually only 3 out of the 20 mothers were Rh negative (15 per cent) and none showed any antibody.

Of the remaining patients there were 4 with a history of infants suffering from haemorrhagic disease of the newborn and 16 with a history of toxaemia of pregnancy. None of these patients showed any demonstrable Rh antibody. It should be noted in this connexion that Javert[15] states that infants suffering from haemolytic disease of the newborn may bleed spontaneously but he makes a clear distinction between this and true haemorrhagic disease.

Summary.

1. The Rh reactions of a series of 280 selected obstetrical cases are reported.

2. The results confirm those of previous workers in cases of hydrops foetalis, icterus gravis and haemolytic anaemia.

3. In 3 cases the titre of Rh antibody was tested during pregnancy and was

found to fall after about the 20th week: it is suggested that this is due to its absorption by the foetus and is a bad prognostic sign.

4. Rh antibody has been demonstrated in cases of death *in utero* (with expulsion of a macerated foetus): this confirms the belief of Henderson and Javert that this is a 4th manifestation of haemolytic disease of the newborn.

5. We have not found evidence to suggest there is any connexion between the Rh factor and any of the following: repeated abortions, congenital abnormalities, haemorrhagic disease of the newborn, toxaemias of pregnancy, and also repeated stillbirths and neonatal deaths other than those due to the 4 variants of haemolytic disease of the newborn.

We are greatly indebted to our many clinical colleagues for supplying us with case histories. We are also indebted to Dr. G. L. Taylor for his constant help with difficult problems, and to Professor T. B. Davie for his interest and criticism.

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Riboflavin Deficiency in Pregnancy

BY

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THE syndrome of riboflavin* (Vit.B_2) deficiency in the human presents distinct clinical features. These are principally maceration and fissuring at the lips and angles of the mouth (cheilosis and angular stomatitis), glossitis, seborrheic accumulations of the naso-labial folds, and certain ocular manifestations. The symptoms can be produced experimentally by the use of a diet deficient in riboflavin[1, 2, 3].

Experiments with animals as well as clinical observations lead to the belief that vitamin deficiencies during pregnancy may cause serious disturbances in the mother, and that they may also effect the development of the foetus. Moore and Brodie[4] observed that female rats kept on a synthetic diet deficient in vitamin B complex frequently abort and resorb their foetuses. A significant relation between prenatal diet, course of pregnancy, and condition of the foetus on delivery has been found by Burke and collaborators[5]. Their study indicates that with inadequate nutrition during pregnancy there is increased incidence of complications and a larger proportion of infants in poor physical condition. A similar study by Ebbs[6] and co-workers showed that malnutrition during pregnancy may lead to serious complications in both the mother and the newborn. The incidence of miscarriages and premature births was found to be increased in women whose diet was poor. Quantitative studies of the vitamin B_1 requirements showed that the thiamine requirements during pregnancy are 3 to 5 times as high as in non-pregnant women (Toverud,[7] Lockhart[8]).

It has been seen that pregnancy can also often reveal latent deficiency diseases. Strauss and McDonald[9] have reported cases of sub-clinical vitamin B_1 deficiency, which became clinically manifest during pregnancy. Other reports[10] as well stress the importance of pregnancy in the manifestation of deficiency diseases.

The present paper deals with the manifestations of riboflavin deficiency during pregnancy. In Palestine they are observed with some frequency in pregnant women. The disturbances occur almost always in women of poor economic circumstances. The patients complain of pain, of a burning sensation of the tongue, and of annoying burning in the upper part of the oesophagus. These and other signs of riboflavin deficiency become apparent during the second half of gestation and regress generally shortly after delivery.

The manifestations of riboflavin deficiency were noted in 21 per cent (190) of cases in a series of 900 pregnant women studied.

* Riboflavin is a necessary constituent of the diet; its richest sources are liver, brewer's yeast, milk, kidney, cheese, eggs, beef, ham, peas.

Clinical Symptoms.

Glossitis: All studied cases (190) manifested glossitis in its various morphological forms. Papillitis (70 per cent), on the tip of the tongue or over its entire surface was the form most frequently observed (Fig. 1). Atrophic glossitis was noted in a large number of cases (25 per cent, Fig. 2). In 5 per cent of the observed cases the tongue showed severe ulcerative changes with desquamation of the lingual mucosa (Fig. 3). The colour of the tongue was purplish or scarlet red. The subjective complaints were pain and burning sensation in the tongue, particularly during ingestion of hot, acid or spiced foodstuffs.

Cheilosis: This symptom, well known as a specific sign of riboflavin deficiency[1], accompanied glossitis in 90 per cent of the cases.

Heartburn: A considerable number (85 per cent) of the patients suffered from severe heartburn. Most frequently the pharynx and the upper part of the oesophagus were involved. Intake of food sometimes caused painful sensations. Examination revealed in a great number of cases redness and atrophic changes of the visible pharyngeal mucosa. The heartburn seriously interfered with the ingestion of food, and thus aggravated further the existing condition of malnutrition. It should be emphasized that the heartburn was not relieved by alkali. In 22 cases an examination of the gastric juice was made. Normal values or slight hypoacidity were found.

Corneal vascularization: Of the entire group of 190 cases presenting signs of riboflavin deficiency, 91 women were examined with a slit lamp.* In 54 (60 per cent) corneal vascularization was found. This manifestation has been claimed to be a specific sign of riboflavin deficiency[2, 3].

Other accompanying symptoms: In addition to aforedescribed manifestations, other symptoms related to riboflavin deficiency were sometimes observed: (1) angular stomatitis in 44 per cent of the cases; (2) seborrheic accumulations on the naso-labial folds and around the eyes in 32 per cent of the cases; (3) vaginitis manifested by more or less abundant discharge and burning, occasionally accompanied by vulvar pruritus, in 28 per cent of the cases. This symptom is sometimes related to riboflavin deficiency (Sydenstricker[11, 12], Jeghers[13]).

Symptoms of other vitamin deficiencies were rarely observed: pellagrous dermatitis was found in 5 cases and neuritic manifestations in 17 cases. No clear-cut symptoms of vitamin C deficiency were seen.

Clinical Course.

All symptoms described above made their appearance almost simultaneously in the second half of pregnancy. Of the 190 cases only 24 were encountered in the first half of pregnancy. The greatest number occurred in the 6th month when 63 cases were registered. The frequency of appearance of the symptoms continued to be high in the 7th and 8th month, as may be seen in Chart I. The majority of manifestations regressed shortly after delivery; the subjective complaints, i.e. pain in the tongue and heartburn, disappeared in the 1st week after parturition. However, a longer time is required for the regression of the anatomical changes in the tongue following confinement. Cheilosis, angular stomatitis and papillary glossitis disappeared gradually during the 1st month following delivery, but atrophic glossitis and corneal vascularization rarely returned to normal even several months after

* We are indebted to Dr. B. Mitterstein and Dr. W. Kornblueth (Ophthalmological Department) for these examinations.

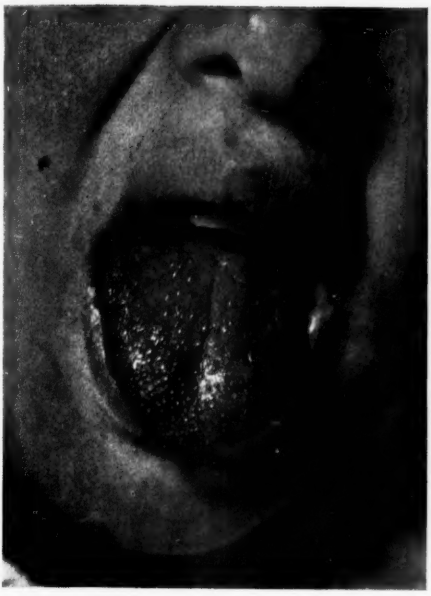

FIG. 1.
Papillitis spread over entire surface of tongue and cheilosis (6th month of pregnancy).

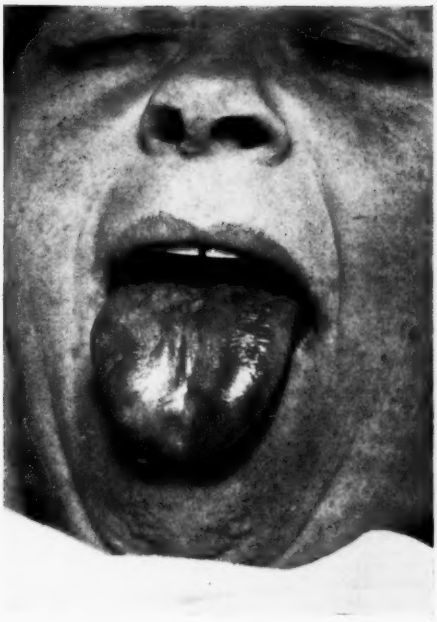

FIG. 2.
Atrophic glossitis (6th month of pregnancy).

FIG. 3.
Desquamation of mucosa with ulceration accompanied by cheilosis (6th month of pregnancy).

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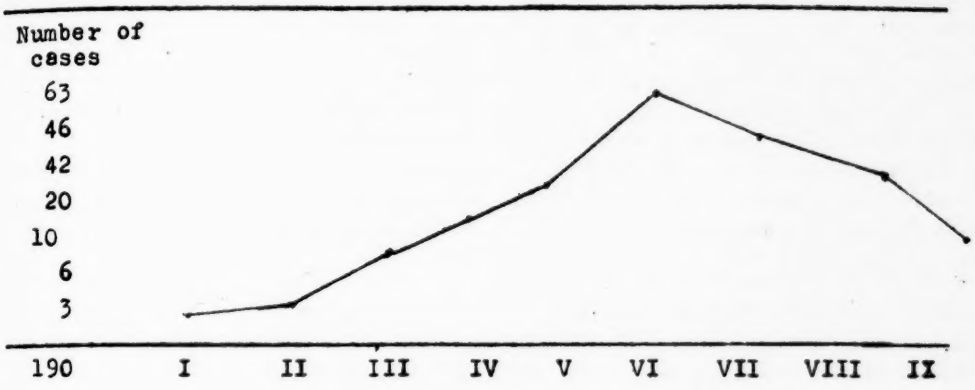

CHART I.
Curve showing the distribution of cases during the various months of pregnancy.

delivery despite the disappearance during the same time of the subjective complaints. Disappearance of symptoms of riboflavin deficiency was also observed following the death of the foetus *in utero*. In 2 cases relief of the complaints followed the death of the foetus *in utero* in the 8th month of pregnancy. It should be emphasized that a large number of the women studied in this series suffered from the described disturbances during successive pregnancies, but remained completely free from these symptoms in the intervals between their pregnancies. All these observations point to the existence of a close relation between the deficiency syndrome and development of the foetus.

LABORATORY TESTS.

The results of the laboratory tests* point, as do the clinical findings, to riboflavin deficiency as the aetiological factor. In 26 cases examined, definite diminution of riboflavin excretion in the urine was found. The average amount of riboflavin excreted in the urine (determined by the method of Snell and Strong[14]) was 95 gamma per litre in the patients, and 360 gamma per litre in a control series of normal pregnant women.

The majority of cases showed an anaemia of a normo- or hypochromic type. This may be regarded as a secondary symptom of malnutrition and iron deficiency.

ECONOMIC AND NUTRITIONAL DATA.

A detailed economic and dietary study was made of the entire group of cases. The study† leads to the conclusion that income in the greater part of our cases was below the minimal subsistence level (less than £.P 1.500 per head per month).

The diet of our patients was below the normal requirement and consisted principally of vegetables, fruits and carbohydrates. The protein intake was extremely low. This diet was particularly poor in

* The laboratory tests were performed by Miss Lea Bychowski, in the Department of Hygiene and Bacteriology, Hebrew University, directed by the late Prof. I. J. Kligler.

† A special report on this subject appeared in the "Inquiry into Poverty and Malnutrition Among the Jews of Jerusalem," published by the Hadassah Emergency Committee, Jerusalem, August 1943.

riboflavin. It has been found that the average daily intake of riboflavin in these women was less than 1.3 mg. This is far below the recommended level for pregnant women of 2.5 mg. (Committee on Foods and Nutrition, National Research Council.)

Therapeutical Assays: In 81 patients therapy with different components of vitamin B complex, and with an extract of yeast (Bevitex‡) (see Table I) was attempted. Twenty-two women were treated with nicotinic acid, given in a dose of 300–500 mg. daily for 5 to 8 days. In 1 case only the subjective symptoms improved, but anatomical changes in the tongue and lips did not regress. Three women were treated with pyridoxine, each patient receiving 200 mg. No effect was observed.

In 30 cases an extract of vitamin B complex (Bevitex) was given for 7 days, the daily amount corresponding to 200–300 gram brewers yeast. Twenty-two cases were favourably influenced, in 8 cases an effect was not noted.

Thirty-three women were treated with riboflavin and striking effects were observed. Thirty-one of these responded favourably to riboflavin given in daily doses of 5 to 15 mg. by mouth for 3 to 7 days (7 of the patients had been previously treated with nicotinic acid without effect). Subjective complaints such as heartburn and pains in the tongue disappeared rapidly following treatment. With continued treatment regression of the anatomical lesions in the tongue and lips took place. The fact should be stressed that riboflavin was effective also in atrophic glossitis, a manifestation which is generally ascribed to nicotinic acid deficiency.[11] The relief of pains in the tongue and the disappearance of heartburn permitted a painless and normal consumption of food. Institution of treatment was followed by rapid improvement of the general condition. The successful results of the riboflavin treatment thus give strong support to the assumption that ariboflavinosis is the aetiological factor in the manifestations which have been described.

‡ Riboflavin, nicotinic acid and Bevitex were kindly supplied by Assia, Chemical Laboratories Ltd., Tel-Aviv; Pyridoxin by Teva, Middle East Pharmaceutical and Chemical Works Co. Ltd., Jerusalem.

Comment.

The outstanding features of riboflavin deficiency in pregnant women are glossitis and heartburn. Frequent accompanying symptoms are cheilosis, angular stomatitis and corneal vascularization. All these manifestations are regarded generally as characteristic of riboflavin deficiency. The greater number of our patients lived in poor economic circumstances and consumed a diet particularly low in riboflavin (the average daily intake being less than 1.5 mg.). The urinary excretion of riboflavin, determined in a number of cases, was found to be far below normal. Further proof of the aetiology of the syndrome was provided by the prompt curative effect of riboflavin therapy. In almost all cases the clinical symptoms made their appearance during the last trimester of pregnancy. This fact is explained by the increase in the nutritional requirements during this period. About two-thirds of the total gain in weight during pregnancy occurs in the last 3 months, because the foetus and its environment grow rapidly during this period. It is obvious that in women whose nutritional state is poor, the increase in nutrition required during pregnancy may lead to gross clinical deficiency. Confirmation of the *rôle* of gestation as a precipitating factor in the deficiency syndrome is found in the following observations:

(*a*) The patients did not manifest clinical deficiency symptoms prior to pregnancy;

(*b*) The syndrome rapidly regressed after delivery or death of foetus *in utero*;

(*c*) The syndrome occurred frequently in successive pregnancies;

(*d*) The syndrome affects especially the pregnant member of the family, the normal members being less sensitive to riboflavin deficiency.

It has been claimed that an increased amount of oestrogenic hormone may favour the appearance of vitamin B deficiency.[15] If this claim is confirmed, it will follow that riboflavin deficiency during pregnancy may be due to the greatly increased production of oestrogens which normally occurs during pregnancy.

TABLE I.

Results of Treatment of Riboflavin Deficiency with Various B-Complex Vitamins.

Treatment	Number of cases	Favourable results	No effect
Nicotinic acid	22	1	21
Extract of yeast (" Bevitex ")	30	22	8
Riboflavin	33	31	2
Pyridoxine	3	—	3

SUMMARY.

(1) In a study of 900 pregnant women, 190 were found to suffer from a glossitis and heartburn. Often these symptoms were accompanied by cheiolosis, angular stomatitis, and corneal vascularization.

(2) These symptoms made their appearance almost always during the last trimester of pregnancy and regressed shortly after delivery.

(3) An aetiological relation between these symptoms and riboflavin deficiency was established by:

(*a*) Economic and dietary investigation,

(*b*) The low urinary excretion of riboflavin,

(*c*) The favourable response to treatment with riboflavin.

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may move through 135 degrees by the posterior shoulder instead of the anterior moving forwards towards the symphysis. If these events occur quickly, as they are particularly apt to do in a multipara (for the significance of which see below), the direction of restitution may escape notice, and the accoucheur may fail to appreciate that long internal rotation of the shoulders has taken place. If the delivery has been by the forceps under fairly deep anaesthesia, the accoucheur may himself restitute the head to the side which he thinks proper before pulling down the shoulders. If he should be inexperienced and if long internal rotation of the shoulders take place, he may not perceive what is happening and he may insist on turning the head to one side while the shoulders are turning to the other. The child's neck will then be subjected to considerable torsion.

Theoretically another variety of long external rotation of the head is possible. After "long restitution" in occipito-positions the posterior shoulder may undergo long internal rotation. In left occipito-posterior positions the movements of the occiput would then be: long restitution 135 degrees clockwise (i.e. to the mother's left) and then long external rotation for another 135 degrees in the same direction, so that it would point first to the mother's anus and finally to the mother's right thigh. This I have not hitherto observed.

How does it come about that the posterior shoulder reaches the pelvic floor before the anterior? In a private communication Professor Miles H. Phillips, to whom I wrote regarding this phenomenon, relates an explanation which Professor Chassar Moir advanced to him in discussing the matter. Professor Chassar Moir wrote: "I fancy the explanation is that the anterior shoulder may become hitched up on the pubic bone and so does not descend into the pelvic cavity in alignment with the posterior shoulder. The obliquely placed posterior shoulder is then pushed right to the front (long rotation) and finally the shoulder that is hitched up on the pubic bone moves to one side and slips down in the normal manner." Professor Phillips directed my attention to William Smellie's advice to prevent the shoulders from hitching on the upper part of the os pubis or sacrum. It is to be found in the Sydenham edition, Volume 1, page 274 and also pages 272, 273 for McClintock's comments. I have not got this edition, but have access to the 1779 edition "printed for W. Strahan; T. Cadell, and G. Nicol, in the Strand; and W. Fox, and S. Hayes, in Holborn." In this edition the advice is to be found on pages 232, 233 as follows: "When the head is come low down, and cannot be brought farther, because one of the shoulders rests above the Os pubis, and the other upon the upper-part of the Sacrum, let the head be strongly grasped with the forceps, and pushed up as far as possible, moving from blade to blade as you push up, that the shoulders may be the more easily moved to the sides of the Pelvis, by turning the face or forehead a little towards one of them; then the forehead must be brought back again into the hollow of the Sacrum, and another effort made to deliver: but, should the difficulty remain, let the head be pushed up again, and turned to the other side; because it is uncertain which of the shoulders rests on the Os Pubis or Sacrum. Suppose, for example, the right shoulder of the child sticks above the Os pubis, the forehead being in the hollow of the Sacrum; in this case, if the forehead be turned to the right-hand side of the woman, the shoulder will not move; whereas if it be turned to the left, and the head at the same time pushed a little upwards, so as to raise and disengage the parts that were fixed, the right shoulder being towards the right-

hand side, and the other to the left side of the brim of the Pelvis, when the forehead is turned back again into the hollow of the Sacrum, the obstacle will be removed, and the head be more easily delivered."

This point receives little attention nowadays. Smellie evidently regarded internal rotation of the head as important in producing a proper movement of the shoulders to enable them to descend easily. If the shoulders stuck, he produced super-rotation of the head by the forceps in order to make them clear the pubis or sacrum and descend. It seems clear that the example he gave, quoted above, was a left occipito-anterior. Now Windemeyer and F. J. Browne[3] have emphasized that the anterior shoulder lies some distance from the midline in occipito-posterior positions, and it therefore seems likely that the anterior shoulder would less frequently be caught by the pubis in such positions than in occipito-anterior positions, in which the anterior shoulder lies nearer to the midline. If this is so, and Chassar Moir's suggestion is correct, then long external rotation of the head in occipito-posterior positions, which, as I have stated above, I have not yet seen, would be equally rare. Finally, one would expect a shoulder to be more readily caught by the pubis in multiparae with flaccid abdominal walls, and they should therefore exhibit long external rotation of the foetal head more frequently than do primigravidae and women with strong abdominal walls. Further observations upon these points may prove interesting.

I wish to offer my grateful thanks to Professor Miles H. Phillips for his valuable criticism of this paper and for pointing out to me Smellie's observations; also to Professor Chassar Moir for the explanation he has offered and which is mentioned above.

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External Endometriosis and Pregnancy
(Report of Two Cases)

BY

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THE increasing practice of microscopic study of gynaecological material has thrown more light on the condition of endometriosis. While all statistics agree on the great frequency of sterility in cases of endometriosis,[1, 2, 3, 4]—Dreyfuss[5] gives 31 per cent and Counseller[6] 32.1 per cent—there is an increasing literature dealing with the association of pregnancy and endometriosis. An excellent review of the subject has recently been made by Scott[7] who added 2 cases of his own.

For clarity, endometriosis is described as internal and external. In the first type the condition is limited to the uterine musculature while the external type includes all other areas containing ectopic endometrial tissue. The two conditions cause different complications in pregnancy, and external endometriosis is more commonly associated with sterility.

Of the 2 cases to be presented the first is one of ovarian cyst of endometrial origin discovered on routine examination at the first visit to the antenatal clinic, while the second is far more unusual, being the only case of tubal endometriosis associated with an intra-uterine pregnancy reported in the literature available at present, which has been limited owing to wartime conditions.

CASE I.

Mrs. E.M.F. Married; age 30. No previous pregnancies.

History. First seen April 17th, 1944. L.M.P. February 4th, 1944. Periods previously lasted 6 to 7 days and occurred every 28 days. Loss heavy, slight dysmenorrhoea. Bowels regular, slight urinary frequency for 2 months. No previous illnesses or operations.

On examination. Healthy woman, heart and chest normal, blood-pressure 130/70.

Urine: Acid, no abnormal constituents present. There was a mass in the right iliac fossa the size of an orange.

Per vaginam. Vulva and vagina normal. Cervix healthy and slightly softened. Uterus enlarged to the size of an 8 weeks' pregnancy pushed back by a cystic mass the size of a navel orange lying in front and to the right of the uterus and continuous with the mass felt in the abdomen.

Provisional diagnosis. Right ovarian cyst and pregnancy.

Operation: May 26th, 1944. *Findings*: The uterus was the seat of a 14 weeks' pregnancy. There was an ovarian cyst the size of a navel orange lying in the right paracolic gutter behind the uterus. *Procedure*: Right oöphorectomy.

Convalescence: Normal. The patient was well sedated and given intramuscular injections of luto cyclin. She was discharged to attend the antenatal clinic; the pregnancy continuing.

Pathology: The ovarian cyst contained a quantity of chocolate substance. It measured approximately 6 × 6 cm. in its collapsed state.

The section of the ovary is that of a chocolate cyst with a most conspicuous decidual reaction.

Comment: According to Scott[7] the ovary is the second most common site for external endometriosis complicating pregnancy. He found in his review of the literature that endometriosis of the recto-vaginal septum, although not so common as ovarian endometriosis, more frequently caused symptoms

FIG. 1.

Microphotograph of section of wall of the ovarian cyst removed from Case 1. The right half shows the ovarian stroma while the left half consists of endometrial glands embedded in a stroma which has undergone a decidual reaction.

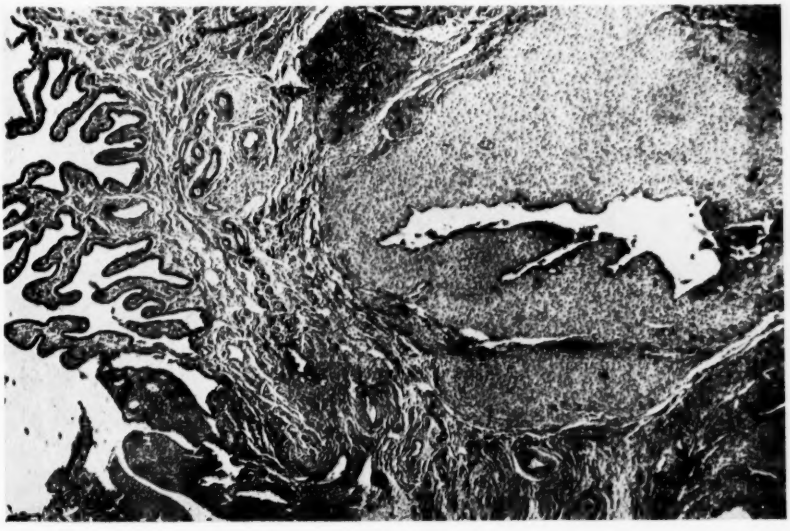

FIG. 2.

Microphotograph of a section of the tube removed from Case 2. The section shows the tubal epithelium lining the lumen and in the wall of the tube an endometrial gland surrounded by endometrial stroma which has undergone a decidual reaction.

in pregnancy than ovarian endometriosis. He collected 7 cases of ovarian endometriosis and pregnancy reported in the literature and added 2 of his own. In the present case the ovarian cyst attracted attention by its size and its true nature was only discovered on microscopical examination. There was no other evidence of endometriosis seen at operation.

CASE 2.

Mrs. O.M. Married, age 34. One normal confinement 7 years ago.

History: First seen January 8th, 1943. Four months previously her periods had begun to decrease and the last normal period occurred in August 1942. She had had scanty shows in September and October and no loss since then. At the time of the suppressed periods she had pain in the right side and severe bearing down. Each month the pain became worse, on the last occasion it was very severe, and she was in bed for 2 weeks. There was no vomiting, her bowels were inclined to be costive at the suppressed period times when she also had some urinary frequency. Prior to 4 months ago her periods were regular lasting 5 days every 28 days. There has been no dysmenorrhoea. There were no previous illnesses, operations or miscarriages.

On examination: Healthy woman, nil abnormal detected in heart, chest or abdomen. Blood-pressure 130/90. Urine acid, no abnormal constituents. *Per vaginam*: Vulva and vagina normal, cervix healthy. The uterus was enlarged to 4 × 3 × 2 inches, and was lying over to the right. It was confluent with a very tender lump the size of a golf ball in the right fornix. The left fornix was clear.

Provisional diagnosis: Right ovarian tumour and probable pregnancy.

Operation: January 15th, 1943. *Findings*: Uterine pregnancy of 3 months duration. The uterus was lying over to the right and partially obscured a tumour 2 × 1½ × 1 inches of the ampullary portion of the right Fallopian tube adherent to the side wall of the pelvis.

Procedure: An attempt was made to resect the Fallopian tube and leave the ovary as it contained the corpus luteum of pregnancy, but haemorrhage was difficult to control, so a right salpingo-oöphorectomy was performed. The appendix was not seen and no attempt was made to inspect the left Fallopian tube and ovary or the pouch of Douglas to avoid excessive handling of the pregnant uterus.

Pathology: The specimen consisted of a Fallopian tube and ovary, the former enlarged in the ampullary portion by a tumour the size of a golf ball. The ovary was the seat of a corpus luteum of pregnancy. Sections of the ovary revealed a well-developed corpus luteum of pregnancy. Sections of the tumour of the Fallopian tube at first revealed the tubal lumen lined by normal tube epithelium and in the wall a mass of decidual cells lying in the muscular coat. Further sections revealed endometrial glands surrounded by decidual cells embedded in the muscular coat.

Sections of the macroscopically normal Fallopian tube showed similar changes.

Convalescence: The patient was well sedated and given intra-muscular injections of lipo-lutein. At the end of 17 days she developed a B. coli cystitis which subsided on treatment with sulphonamides. The urine became sterile on culture and the patient was discharged on March 3rd, 1943.

Subsequent course of pregnancy. Normal till June 11th, 1943, when the patient complained that she did not feel well. The presentation was left occipito anterior; the head was low in the pelvis; blood-pressure 160/110; cloud of albumin and B. coli were present in the urine. The urine became sterile and free from albumin after giving 12 gm. sulphathiazole, and the blood-pressure fell to 130/90.

Labour: Began on July 7th, 1943, and was normal. She was delivered of a living male infant 6 pounds, 1½ ounces.

Puerperium: Normal.

Post-natal examination: September 8th, 1943. Pelvis normal and the patient stated that she had begun to menstruate normally and had no pelvic symptoms. A verbal report on October 30th, 1943, revealed that she felt well, nevertheless a guarded prognosis was given both as regards further pain and the possibility of further pregnancies.

Comment: As several sections of the biopsy material were necessary to establish the diagnosis an attempt was made to review the literature on the subject.

Endometriosis of the Fallopian tube has been noted more frequently of late,[8, 9, 10, 11].

Haydon[4] reviewed a series of 569 cases of endometriosis and found that in 16 (2.8 per cent) the lesion was in the Fallopian tube. Emphasis has been laid on the involvement of the tubal epithelium. Frankel and Schenck[8] consider that ectopic endometrium in the Fallopian tube is the cause of ectopic gestation. Their evidence is based on the study of serial sections of Fallopian tubes removed for ectopic pregnancy and they noted chiefly changes in the tubal epithelium or endometrial tissue in the tubal lumen which had undergone a decidual reaction. They report 1 case in which endometrial tissue was found at the abdominal end of the Fallopian tube and another in which the tissue was seen at the junction of the ampullary and infundibular portions and they quote a case of Hohne in which the endometrial change was found in the intramural portion of the Fallopian tube. Marchetti[9] reported 2 cases in which lining of the tube was replaced by endometrium. The change in both cases involved the distal two-thirds of the tube. Both patients had previously borne living children but neither was pregnant at the time when the condition was observed.

Philipp and Huber[11] consider that adenomyosis occurs chiefly in the interstitial portion of the Fallopian tube and is extremely rare in the more lateral areas. They state also that in more than 20,000 serial sections there was a continuation with the corporeal endometrium, and they compare the condition to adenomyosis uteri interna with the proviso that in the latter condition the endometrium permeates deeply into the myometrium, whereas in the former the spread is lateral, the transitional area between uterine and tubal mucosa being pushed further and further outwards.

This case presents several features of interest:

(1) It is the only case of tubal endometriosis and intrauterine pregnancy which the author has been able to trace.

(2) The site of the tubal involvement was unusual, the muscular coat and not the epithelium being involved.

(3) The ampullary portion of the tube was attacked and not the more usual interstitial area.

(4) The diagnosis was incorrect. This was so in most cases of uterine pregnancy and endometriosis reported in the literature. At first on the microscopic report one was inclined to think that the condition was one of intra- and extrauterine (tubal) pregnancy.

(5) That pregnancy occurred and implantation was in the uterus can probably be explained by the fact that the area affected was the tubal muscular layer and not the epithelium. A lesion in the tubal epithelium usually causes partial or complete blocking of the lumen, a condition which would favour ectopic gestation or sterility. The possibility of external migration of the ovum, however, must not be forgotten.

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Some Curiosities of Mammalian Reproduction

Part 3.—Mammals that Produce Uniovular Litters *

BY

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A curious phenomenon has long been known by entomologists to be displayed by certain parasitic Hymenoptera. This phenomenon was first investigated by Silvestri. He found that "in the genus *Litomastix*, in which the eggs are laid in the body of a caterpillar, a single egg divides very early into a large number of separate embryonic primordia, each of which produces an adult insect. No matter how many individuals are derived from one egg—*the numbers may be even a thousand*—they are of the same sex." No mammal can claim any achievement so dramatic as this but some of them have succeeded in producing some rather astonishing results in the direction of begetting uniovular litters.

MAMMALS THAT HAVE HAD TO REDUCE THE SIZE OF THE FAMILY.

THERE have been many theories put forward to account for the fact that some mammals produce large litters and have large families while some have only small ones.

Herbert Spencer (1899) had a theory. "According to this theory the power to sustain individual life and the power to produce new individuals are inversely proportional, a conclusion which is summarized in the generalization that Individuation and Genesis vary inversely."

F. H. A. Marshall (1922) has also formulated a theory. "Broadly speaking, the average number of young produced in a litter in any species of mammal is inversely proportional to the average size of the animals belonging to that species." In homely language, these two theories postulate alternatively:

(*a*) that long-lived mammals have smaller families than short-lived ones, and

(*b*) that big mammals have smaller families than little ones. But neither of them taken separately nor both of them considered together would seem to provide a very satisfactory solution of the business. Indeed it would be very interesting to learn the opinion of the Shrew concerning Spencer's dictum. For a Shrew, born in May or June, is dead before its second Christmas Day comes round. In its short life, it may perhaps produce two litters. What then would the Shrew say when it learned of the elderly female Rabbit, perhaps a dozen years old, that had regularly produced litters of five or so several times a year? It would be equally interesting to know what that tiny mammal, a Pipistrell bat, would think of Marshall's theory. For the Pipistrell produces only one offspring once a year and so would feel dissatisfied with the dicta of science when it considered the case of the bulky sow, followed at frequent periods by recurrent and ample litters of piglets. Probably neither the Shrew nor the Bat would consider the theories entirely satisfactory or of very general application.

At the present moment there are, I believe, committees appointed by the Government and composed of especially gifted and eminent persons, considering the question of increasing the birth-rate when this

* Lloyd Roberts Lecture—Part 3.

war is over. The following quotation is taken from an Arris and Gale Lecture delivered during the European war of 1914–18. It was written without regard to human problems. "*Large families can therefore only be indulged in, as a rule, by animals the females of which may be exempted from any very exacting activity during pregnancy*. Such is a general axiom among the mammals and, leaving altogether the stock with which we are most concerned, examples of its truth are readily furnished in many Orders. Herbert Spencer gave much thought to the well-known instance of the relative fertility of the hare and the rabbit: Much of his speculation was no doubt true; but we must not overlook the fact that a doe rabbit's home is safe in a burrow, while the female hare has no such protection, and the same cause that has led to the reduction of the hare's litter has been at work, with even greater force, among the Ungulates. Again, in aquatic life the same disability is felt and the picture of the pelagic life of the whales makes the second axiom—that, *where there is no nursery there will be no large families* —more real." This was written as part of an essay that attempted to outline "The Influence of the Arboreal Habit in the Evolution of the Reproductive System." The thesis it sustained was that since a female animal that lived a truly arboreal life was severely handicapped in its activities when pregnant of a large litter and could not nurse helpless young in the tree tops, the Primates had tended to reduce the number of young produced at a birth and so limited the size of the family. Perhaps the thesis may be extended from the Primates as an interesting mammalian phylum in general, to Man, one of the more interesting members of the phylum, in particular. It may be that the gifted scientists and others, who are now planning for the post-war increase in the number of births, would do well to bear in mind these two axioms: (1) Mammalian females, if they are to produce large families, must be "exempted from any very exacting activity during pregnancy" and (2) they must be provided with a safe retreat and a satisfactory nursery before much can be expected from them in the way of producing the large families that the statesmen appear to think so desirable at the moment.

There is a type of writer, who in certain literary activities impinges on biological subjects, and who never tires of telling us of the prodigality with which Nature produces a vast excess of offspring; an excess that can never hope to attain to maturity or even to enjoy life at all. I do not think it requires great erudition to detect the underlying implications that attract some people to such a view of the workings of Nature. Were there no excess of offspring to be weeded out what would happen to the fundamental teaching of the Struggle for Existence? What would become of the Doctrine of the Survival of the Fittest? Surely we must have Nature red in tooth and claw else the redness of our own talons might be deemed as something not quite in harmony with the ways of Nature!

Perhaps as a corrective to this rather fashionable mode of thought concerning the wasteful way in which Nature permits offspring to be born only to be eliminated in bitter and bloody struggle, it may be well to consider the converse of the problem. Most assuredly there is another side to the picture, for nothing is more striking in the story of mammalian reproduction than the harmonious adaptation of structure and function to limit the number of offspring produced by those mammals whose habits and environment prevent them from having access to a natural nursery in which the offspring may be tended by the mother.

It is easy to picture the outstanding

factors of environment and habit that deprive the mammalian mother of a natural nursery. If the mother lives in the tree tops she can neither be pregnant with a large litter nor deal with a large number of helpless offspring when born. Mammalian nest building though a widespread habit with arboreal marsupials, rodents and primates, does not solve the problem for animals of any considerable size. Arboreal American opossums (*Didelphis*, etc.) and Australian arboreal phalangers (*Trichosurus*, etc.) may overcome the difficulty by resorting to such expedients as intertwining prehensile tails or carrying the young in a pouch; but these things are no more than makeshifts at the best. The arboreal primates and arboreal edentates have solved the problem by reduction of the number of offspring produced at a birth.

Again if a mammal leads a completely pelagic life the mother finds no nursery and all the Cetacea have had to limit the litter to single births. Defenceless animals that live in open spaces and have to seek safety in instant flight in the face of danger are in the same case and many cursorial ungulates, rodents and marsupials cannot afford to be pregnant of or to beget multiple offspring. And lastly, volant animals, like the bats, that must needs carry the helpless young with them as they fly in search of food, have come under the ban of prohibition and have to be content with one or perhaps two at a birth.

It is only the strong and the well-armed, or such of the weak and defenceless as happen to have homes and safe retreats in lairs or holes or burrows or nests that can afford large litters that they may nurse and tend in safety and at their leisure.

Now if circumstances of habit and environment dictate that the number of offspring produced at a birth should be only one or perhaps two, that the mother may nurse and defend, several anatomical and functional changes must be brought about.

In the first place, it is obvious that the number of ova shed at any period of ovulation must be reduced. If multiple ova are passed into the female passages at any act of ovulation their fertilization is guaranteed, for there is no reduction in the vast number of spermatozoa awaiting them.

Next, it is necessary that a definite single-pregnancy type of uterus should be reshaped from the common mammalian multiple-pregnancy type. And lastly, since a full series of mammary glands is no longer necessary, there will be reduction in their number.

It is apparent that the mammals producing single offspring, including such diverse forms as some primates and edentates, most cetacea, certain ungulates and rodents and the bats, have no phylogenetic or taxonomic affinity. They constitute, in this connexion, a group of animals bound together by a single functional bond. They are animals that, because of habit and environment, have had to reduce the typical mammalian litter to the production of a single offspring at a birth. It is this plain physiological fact that renders the striking similarity of their structural and functional adaptation so instructive. Changes are effected harmoniously in the ovary, the female reproductive tract and in the mammary system. Here the changes brought about in these three systems can be reviewed only briefly.

The primitive mammal was almost certainly endowed with multiple functional mammary glands and nipples. All the primitive non-arboreal insectivora possess a full series. The tenrec of Madagascar (*Centetes ecaudatus*) has no less than 11 pairs of mammary glands and nipples and litters as large as 21 have been recorded.

In all the typical primates the functional

mammary glands have been reduced to a single pair, pectoral in their position. In such edentates as the sloths and anteaters only one pair of pectoral mammae is present. In the perissodactyle ungulates the single pair is typically inguinal in position, as is the reduced series of single-offspring cursorial rodents. The mammary glands of the pelagic whales and dolphins are also reduced to a single pair and these glands are situated on either side of the vulva. The volant bats again select a pectoral site for the single pair of functional mammae retained. The general principles involved in the business may be summed up by saying that if any mammal, no matter what its phylogenetic status may be, has, by habit or environment, to adopt single-offspring pregnancy, the series of mammary glands will be reduced to a single functional pair and their site will be that dictated by the mother's convenience in nursing. No mammal has so far transgressed, nor is likely to transgress, the great law of general bilateral symmetry as to reduce the mammary series to a single unit.

As for the necessary modification of the primitive mammalian reproductive duct system, it is remarkable how similar are the stages rehearsed by all single-offspring mammals and how strikingly similar are the end results produced despite any sort of phylogenetic kinship.

In the whole course of the female genital ducts (Müllerian ducts) there are, in the embryos of all mammals, three very distinct portions separated by definite landmarks. The most cephalic portion of the ducts stretches from the abdominal ostium to the point at which the gubernacular strand of the ovary (round ligament) crosses the duct. This cephalic part lies primitively in the long axis of the body and is destined to become the so-called Falloppian tube. The next part is embraced between the point of attachment of the gubernacular strand and the place at which the two ducts of the opposite sides of the body become approximated in the midline and enveloped in the tissues of the "genital cord." This is the part that tends to lie transverse to the long axis of the body and it forms the uterine cornua of the adult. The last part, confined in the genital cord, fuses with its fellow of the opposite side and forms a single median chamber—the corpus uteri (See Fig. 19).

The most distal sections of the female ducts (Falloppian tubes) are destined to become the true oviducts in all mammals, for they convey the ova from the ovaries to the pregnancy chamber. The middle portions, in the typical mammals that produce multiple young at a birth, become the bilateral pregnancy chambers or cornua uteri. The terminal median portion becomes the common passage through which the foetuses leave the uterus for the vaginal canal at birth (See Fig. 20). Since in the mammal that produces only a single foetus at a pregnancy the long double pregnancy chambers cease to be necessary they undergo a steady reduction in the stages of ontogeny. This shrinkage is marked by the increasing approximation of the point of attachment of the gubernacular strand and the corpus uteri itself. In the end the two cornua shrink inwards towards the corpus uteri to such an extent that they cease to exist as entities and the gubernacular strand becomes attached to the sides of the corpus uteri itself. With the diminution of the cornua the corpus uteri enlarges to form the single median pregnancy chamber destined to be the nidus for the single foetus (See Fig. 21). In this way the Falloppian tubes or oviducts join directly with and open into the corpus uteri in such widely diverse animals as man and monkeys, armadillos (Fig. 22), sloths, anteaters and certain other edentates, some bats (Fig. 23) and other single-offspring mammals. In all these forms the gubernacular strands

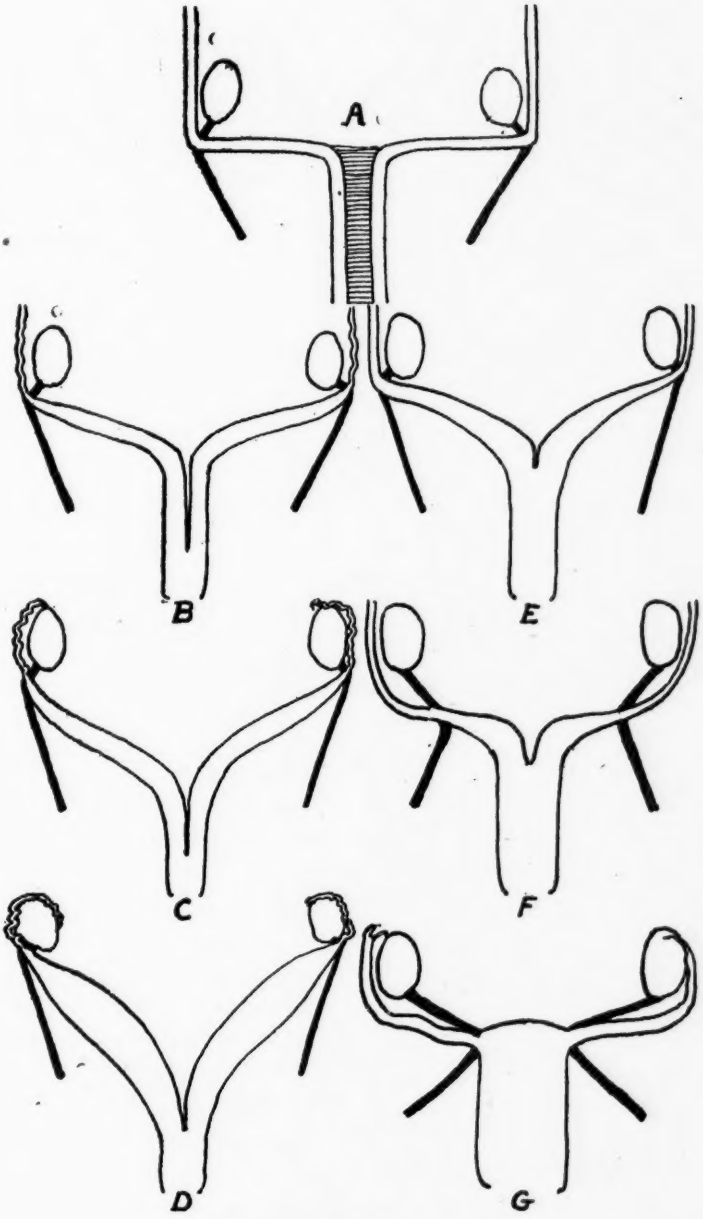

FIG. 19.

Developmental stages of (B.C.D.) the multiple-pregnancy and (E.F.G.) single-pregnancy type of uterus from the primitive condition shown in A.

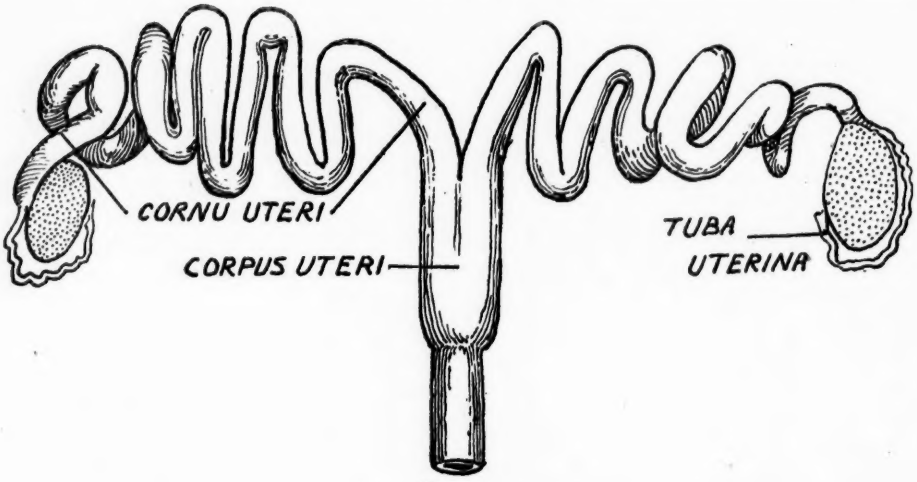

FIG. 20.

The multiple-pregnancy type of uterus, with large cornua, small body and minute tubes. The uterus is that of a sow.

delimit the Falloppian tube segments from the corpus uteri segment and the round ligament of the ovary and the round ligament of the uterus, instead of being in a direct line are at an acute angle to each other—the angle being formed by the complete regression of the cornua uteri into the corpus uteri. The cornua have disappeared, not by fusion to form the large corpus uteri as is often assumed by human anatomists, but by shrinkage towards the corpus uteri. If any portions of the typical mammalian cornua persist in the corpus uteri of the single-offspring mammals, they are to be looked for in the short pars uterina tubae.

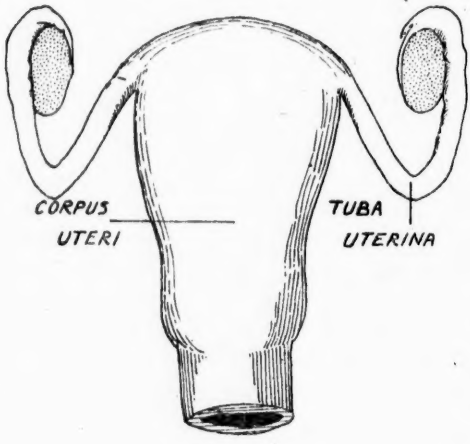

FIG. 21.

The single-pregnancy type of uterus, with large body and tubes but no cornua. The uterus is that of Homo.

When we come to seek for facts regarding the changes in the ovary whereby a reduction of the number of ova shed at a period of ovulation is brought about, we have no such satisfactory basis for assurance as we have in the case of the mammary system or in that of the female genital ducts. There are not sufficient facts recorded to enable us to write a history of the structural and functional changes in the ovary that ultimately lead to the production of only a single ovum at the time of the ovulation. Strangely enough it is only concerning two of the more outlandish

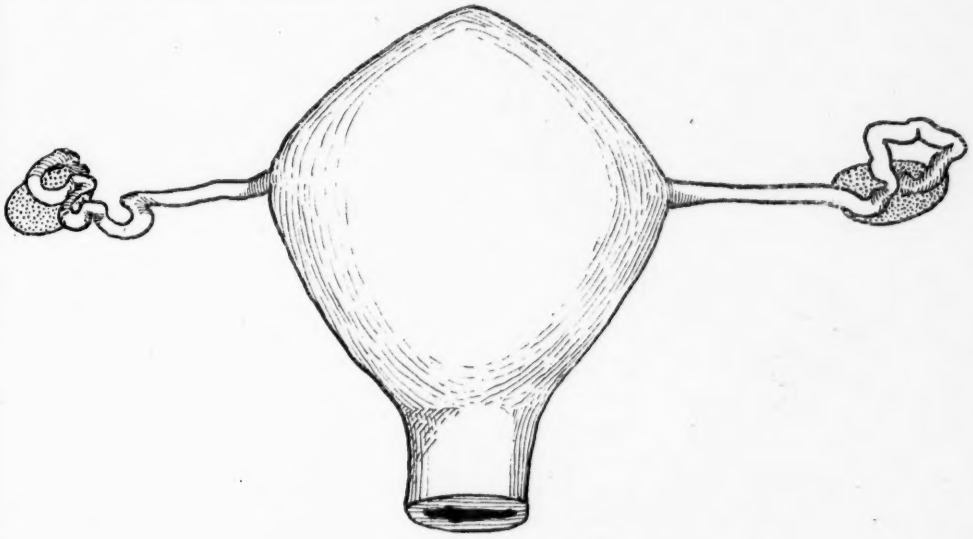

FIG. 22.
The single-pregnancy type of uterus of an armadillo.
(After Newman.)

members of the single-ovum mammals—armadillos and bats—that we have any really definite knowledge. We cannot hope for a series of overt demonstrations of the actual number of ova shed from the ovaries during the period of ovulation in a wide series of mammalian types. But fortunately a visible record always persists of the actual shedding of the ovum. The bulky corpus luteum is always to be found in the ovarian follicle from which the ovum was shed. (See Fig. 24.) It is therefore necessary to rely upon the findings as to the number of corpora lutea present in the ovaries of pregnant animals in order to estimate the number of ova shed from the ovary during the period of ovulation. Fortunately in the case of at least 2 mammals we have direct evidence that the production of ova has been reduced and that only one is normally produced to become fertilized and so to provide the basis of the ensuing pregnancy.

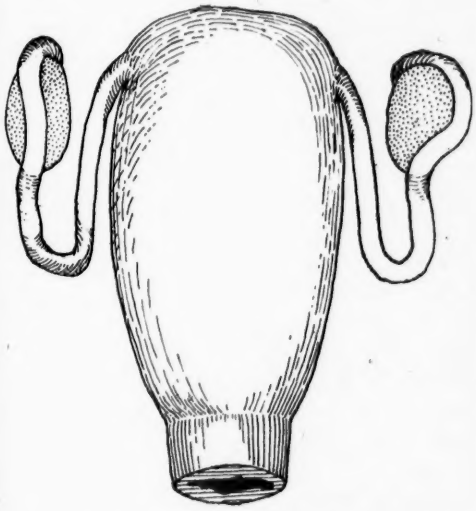

FIG. 23.
The single-pregnancy type of uterus of a phyllostomid bat. (After Robin.)

THE REPRODUCTION OF THE EDENTATES.

The edentates are, as a group, no great favourites with the systematic mammalo-

gist for they do not fit very readily into his orderly schemes of classification. Certain characters are common to them all, but many of these common characters are such as might be expected to distinguish the existing members of almost any stock that

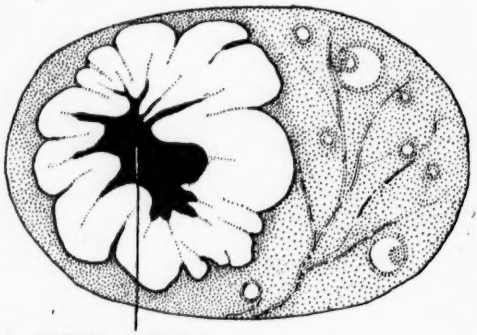

FIG. 24.
Outline drawing of a section of an ovary to show the single corpus luteum of pregnancy.

has fallen out of the race for progress and has become phylogenetically senile. Specialized diet, specialized habit and specialized anatomical developments distinguish them all and of all of their specializations it may be said that they are such as lead to nowhere in the mammalian march of progress. Perhaps it is for this very reason—that they are possibly a mammalian job lot—that they are of most interest to us in connection with their reproductive story. Most probably all the members of the Order that inhabit the New World are bound together by real, if not very immediate, bonds of affinity and fortunately we have every assurance that the group of the armadillos, with which we are more especially concerned, are all near akin.

One very definite specialization that the sloths, the anteaters and the armadillos of the New World have all embarked upon is the development of a simple, globular single-pregnancy type of uterus and a reduced series of mammary glands and nipples. Quite obviously, from the point of view of the relation of structure to function, they have all carried out all the anatomical changes that are characteristic of mammals that have reduced the size of the litter. Apparently no detailed accounts of the whole reproductive history of the sloths (*Bradypodidae*) or of the anteaters (*Myrmecophagidae*) have been published. We do, however, know that among the sloths a typical single-pregnancy uterus and a mammary series reduced to a single pectoral pair of glands and nipples have been uniformly achieved. The same generalization holds good with the anteaters and, in the absence of any evidence to the contrary, we may assume that in all of them only one offspring is produced at a birth, as is the case with those few species concerning which there is any definite information.

It is only concerning the reproduction of certain species of armadillos that all the essential facts are definitely known and extremely strange facts they are. Although it is so long ago as 1885 that the curious story was first told, more than a quarter of a century elapsed before renewed scientific researches made it impossible to ignore or to disbelieve in the occurrence of the strange happenings that H. von Jhering had first claimed to be realities.

Von Jhering had examined 2 pregnant females of the species known as *Tatusia hybrida* that inhabits Argentina and whose local vernacular name is Mulita. He found in the simple uteri of both these females no less than eight embryos and these embryos were all enclosed within one chorionic membrane. More than this, all the embryos of both females were of the same sex, for both sets consisted entirely of males. The facts of this original finding were published as a brief note in 1885 and

in the next year the case was reviewed in another communication and now the almost unavoidable conclusion was arrived at—that each of these sets of 8 identical, same-sexed embryos had been derived from a single fertilized ovum. Von Jhering postulated the almost unbelievable, yet almost inescapable thesis that the entire litter of 8 embryos of *T. hybrida* had somehow been derived from the subdivision of a single ovum into 8 separate and identical individuals. Unfortunately, and owing to a stupid mischance, this strange finding did not receive the attention it deserved. Von Jhering had sent the ovaries of a female armadillo of another species (*T. novemcincta*) of the same genus to Rosner for examination and in 1901 an account of the microscopical structure of these ovaries was published. In this paper Rosner claimed that the only thing that was strange about the business was that the ripe ovarian follicles of this animal frequently contained multiple ova. According to Rosner's finding, all that happened was that the rupture of an ovarian follicle in the act of ovulation released many separate ova instead of the usual one and that the embryos present in the uterus were the products of separate ova in the manner usual among mammals producing multiple offspring. It therefore became accepted that the separate ova instead of having come from an equal number of separate follicles had in the case of this animal been matured within and released from a single follicle, but otherwise the process of reproduction was normal. Although this account of the process as given by Rosner entirely overlooked the outstanding fact that all the embryos in both litters were of the same sex, it appeared to fit into the general body of knowledge of the formation of multiple pregnancies of lower mammals and as a consequence the interest in the peculiar reproductive habits of the armadillos lapsed for a time. It was not until 1909 that M. Fernandez re-examined the embryological history of *T. hybrida*. His researches revealed the fact that though 8 embryos constitute the usual litter, the number of young produced at a birth varied from 7 to 12. But he also showed quite conclusively that only 1 ovarian follicle, containing 1 ovum, and, subsequently, a single corpus luteum was involved in any individual pregnancy. Moreover, he made a thorough examination of the early stages of embryonic development and showed how the embryonic rudiment of the original single blastoderm vesicle underwent a process of fission. The ectoderm of the embryonic plate produces outgrowths from its central area and these outgrowths become in their turn areas of growth and development which, by extending away from the central area, form the bases of independent embryonic differentiation. At first, the embryonic area gives rise to two outgrowths at opposite sides of the little disc of cells. Next, two more are produced on an axis at right angles to that of the first two. Later in the intervals between these 4 prolongations of the embryonic area, 4 more outgrowths take place as a rule in *T. hybrida* and evidently in some instances 4 more are added to the series. Each one of these separated outgrowths then passes through all the stages of individual embryonic development and in the end 8 or 12 identical embryos are developed within a common chorionic cavity. Each has its own umbilical cord and each its own placental area differentiated in a common zonular placenta. Each is in its own amnion but the separate amniotic cavities are all connected with the original common point of origin of all the embryos, by a series of small amniotic canals.

It would seem that in *T. hybrida* the cleavage of the original embryonic plate is

normally into 8 or 12 and that when odd numbers of foetuses are present later on in pregnancy the reduction occurs as a result of overcrowding in the uterus and subsequent abortion of some of the number. There would seem to be some disadvantages in the attempt made by this species of armadillo to produce eight or a dozen foetuses and to accommodate them in a uterus that seems so obviously designed to accommodate only one.

In the same year (1909) as that in which Fernandez described the strange happenings in *T. hybrida*, H. H. Newman and J. T. Patterson published a preliminary report of their investigation into the reproductive history of an allied species (*T. novemcincta*) the Peba or Nine-banded armadillo of Texas. In this species the processes are exactly the same as in *T. hybrida* save that when the embryonic plate has produced its 4 outgrowths no further subdivisions are formed. The result is that in this species 4 identical same-sexed foetuses are produced at every pregnancy. Newman and Patterson were careful at the outset of their enquiries into the stages of embryological development to determine the fact that "*there is never more than one true corpus luteum in the ovaries of a pregnant female.*" In *T. novemcincta* as in *T. hybrida* the ideal number of same-sexed identical foetuses is not invariably present. In Newman's series of over 200 pregnant uteri there were two in which only 3 were present and in one of these there were obvious traces of the aborted fourth member. In three cases five foetuses were present and in one of these the remains of a degenerating sixth embryonic rudiment were present.

Perhaps few facts in systematic zoology are more puzzling than that demonstrated in the profound anatomical and physiological differences between two such obviously nearly allied animals as the spotted hyena (*Hyaena* (*Crocuta*) *crocuta*) and the striped hyena (*Hyaena striata*). The spotted hyena, as we have seen, contradicts every rule of ordinary mammalian sexual development, while the striped hyena is perfectly normal in this regard.

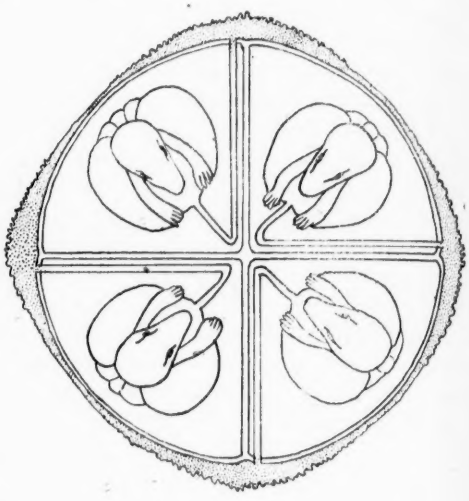

FIG. 25.

The four uniovular foetuses of *Tatusia novemcincta* to show their symmetrical arrangement in the uterus. (After Newman.)

The Mulita armadillo and the Nine-banded armadillo are so nearly allied as to have been regarded by some mammalogists as merely local varieties of the same species.

It is surely a remarkable thing that these two creatures should have resorted to this strange method of producing multiple offspring from a single ovum and still more strange that while the one species produces 4 in a litter, the other has elected 8 or 12.

The genus *Tatusia* is not the only assemblage of South American armadillos, for other forms, distinguished by certain characters that will be discussed later, are embraced in nearly allied genera. Of these, the members of the typical genus *Dasypus* are of outstanding interest. The reproductive

history of the 2 species, the Six-banded armadillo (*D. sexcinctus*) and the One-banded armadillo (*D. gymnarus—Xenurus unicinctus*) has been studied with more or less completeness. Von Kolliker and Chapman are agreed that these species normally produce only a single offspring at a birth, but the birth of two young has been recorded in the case of *D. sexcinctus* in the Philadelphia Zoological Gardens. But the most disconcerting of all the members of this genus is the Hairy armadillo or Peludo, *D. villosus*. In 1915, Fernandez announced the curious finding that in this species 2 foetuses commonly occupy the uterus and these foetuses seem to present every evidence of being derived from a single ovum. The 2 foetuses appear to be contained in a single chorion, separated from each other by what at first sight seems to be their fused amniotic membranes. Each foetus has its own umbilical cord and share of a zonular placental area. But the strange discovery that Fernandez made was that in the first 10 pregnancies he examined, the 2 embryos were both males in one case, both females in 2 cases and *in seven cases they were of opposite sex*. Although the embryos appear to be enclosed in one chorion and although the general appearance of the pregnancy resembles so much that typical of the members of the genus *Tatusia*, the fact that the pairs of embryos are not invariably of the same sex seemed to prohibit their origin from a single ovum. Fernandez examined in all 34 uteri containing embryos in every stage from primitive streak formation to full term. He found that the 2 embryos quite definitely started from 2 separate ova and that these 2 embryos crowded together in the simple uterus had become so closely approximated during development that their membranes had fused together and become thinned out over the area of fusion to such an extent as to produce the appearance of a single chorionic vesicle containing two embryos separated only by their amnia. Two further interesting facts were revealed by Fernandez during this investigation, for he found 5 cases out of his 34 pregnancies in which only one embryo was present in the uterus. He also noticed that in young females that had never been pregnant the uterus still showed evidence of bicornuate structure.

What sort of generalization can possibly be deduced from this strange assemblage of facts? Obviously any suggestion of generalization can be but little better than guesswork. But there are one or two deductions that may be drawn with comparative safety from the anatomical findings.

In the first place it seems justifiable to assume that all members of the *Bradypodidae*, *Myrmecophagidae* and *Dasypodidae* alike have in their phylogenetic story gone through the phases of structural adaptation of uterus, ovaries and mammary glands typical of mammals that produce only one offspring at a pregnancy. It is only of the *Dasypodidae* that we know sufficient facts concerning reproduction to obtain any insight as to the changes that have happened or to make even the most tentative guess as to the causes of their happening. Of the family *Dasypodidae* it is only of the two genera *Tatusia* and *Dasypus* that we have sufficient *data* to make dogmatic statements. So far as the different species of these two genera that have been examined can tell us it seems true to say that members of the genus *Tatusia* produce multiple, same-sexed uniovular embryos, while those of the genus *Dasypus* produce either single embryos or two that, in the case of the only species so far fully studied, are, or may be, opposite sexed, and are derived each from a separate ovum despite their deceptive monochorial appearance. Anatomically, the differences between members of the two genera *Tatusia* and

Dasypus, as these genera are generally defined, may be summarized as follows:

TATUSIA.

There are milk precursors of the permanent teeth.

There are only 4 digits on the manus and 5 on the pes.

A pair of inguinal mammary glands is present in company with a pair of pectoral glands.

The uterus does not show any sign of the primitive cornua.

DASYPUS.

There are no remains of a milk detention.

There are 5 digits on both manus and pes.

Only a pair of pectoral mammary glands is present.

Presence of uterine cornua indicated in uterus of young female.

It may be correct to state that of the armadillos, *Tatusia* " is the most aberrant form " (Flower and Lydekkar, 1891), but it retains at least one primitive feature in the possession of a partial milk dentition and probably another in having 4 instead of 2 mammary glands. Both genera are geologically ancient and all their known ancestors are confined to South America where remains of members of the existing genera are present in pleistocene deposits. Unfortunately, no definite conclusions as to the habits of their more remote ancestors in the Miocene of Santa Cruz in Patagonia or in the earlier Eocene beds can be safely drawn from their fragmentary remains. We can therefore only guess at the factor that caused them, at some remote period in their story, to bring about all the anatomical changes that are typical of a single-birth pregnancy. Perhaps the most likely guess is that, since all the members of the *Myrmepophagidae*, save one, are arboreal and all the *Bradypodidae* are rigidly confined to a life in the tree-tops, it was the arboreal habit that was the determining cause. Although it might seem that armour-plating is incompatible with arboreal life it must not be forgotten that it is possible that this was more highly developed subsequent to the descent from the trees and with the adoption of terrestrial life. And it must not be overlooked that among the armoured Edentates of the Old World (*Manidae*) many of the Pangolins or Scaly anteaters are true tree-climbers although a few of them have abandoned arboreal habits and have become terrestrial and burrowing animals. The existing armadillos are terrestrial creatures and all accounts of their habits are agreed upon the expertness of their methods of burrowing and upon the depth of the retreats in which they have their homes and produce their young. I know of no account of their life histories that suggest any possible remaining aptitude for climbing but that is not surprising in a group of animals so little studied in intimacy.

Whatever it may have been in habit and environment that dictated all the anatomical changes of uterus, mammary glands and ovaries towards the end of begetting a single offspring at a birth, it is very evident that the present circumstances of habit and environment make no such demand. Beyond all animals, the one that has a nursery safe in the depths of a burrow can afford to produce large litters. It might be hazarded that the members of the subfamily *Tatusiinae* had, at an earlier phylogenetic stage, so specialized in uniovular ovulation that when change of circumstances had resulted in the possibilities of dealing with larger litters the only method of producing them was by the subdivision of the single ovum. The difficulty of the single pregnancy uterus was overcome by the extraordinary mechanical and symmetrical arrangement of the resulting embryos in the uterus. But I know of no observation concerning the method of suckling of the numerous young at the limited number of nipples. That the dis-

parity between the number of functional mammary glands and the number of offspring produced at a birth is no insuperable obstacle to the successful rearing of a family we know from the case of the guinea-pig. In this animal there is but a single pair of mammary glands, but the number of young in the litter may considerably exceed this. In this connexion it is worth noting that both the guinea-pig and the Tatusias have exceptionally long gestation periods. The guinea-pig is pregnant for nine weeks, the Peba armadillo for twice that period and the milk requirements of young animals born mature and after prolonged periods of gestation are well known to be less than those of more immature offspring.

Of the members of the sub-family *Dasypodinae* it might be hazarded that they are still capable of producing more than one ovum at the period of ovulation and that frequently 2 at least are shed and fertilized. The only difficulty to be faced is the implantation of 2 pregnancies in the simple uterus adapted for the accommodation of only a single foetus. Here resort is made to the same sort of symmetrical packing as is adopted in the case of the Tatusias with the result that diovular foetuses appear to be monochorial.

Two speculations suggest themselves from a study of the reproduction of the armadillos. The first is that caution must be exercised before apparently monochorial foetuses are diagnosed as being necessarily uniovular in origin. And the second is that the production of uniovular twins might be expected to be confined to those animals that have carried out all the readjustments of uterus, mammary glands and ovaries associated with the habitual begetting of a single offspring.

Human and Other Twins.

There would seem to be but little temptation to produce more than one offspring from a single ovum in cases in which many ova are shed in a single act of ovulation. Indeed we know that in the mammals that produce large numbers of offspring at each pregnancy there is often, if not invariably, a shedding of ova in excess of the number of young that are actually born. There are ova enough and to spare to provide for these multiple pregnancies for not all the ova that are fertilized ever reach maturity. Some are aborted in early stages of development by overcrowding in the uterus. Some perish by lack of a sufficient blood supply. Some are too late in their arrival in the uterus. Even when all the embryos are successful in arriving at maturity and all of them have succeeded in being born they may still be in excess of the number that are destined to grow up. It is well known that some of the marsupials produce more embryos than they have nipples in the pouch and since the immediate grasping and retention of a nipple is essential to life some of these excess embryos inevitably perish. As a general rule therefore we may say that multiovular mammals tend to produce ova in excess of the young normally reared as the result of a pregnancy. There is no need to subdivide a single ovum in order to provide a litter.

But if any group of mammals has established the physiological rhythm of producing only one mature ovum during each period of ovulation its only possibility of producing multiple embryos is to subdivide the single egg. This is what the armadillos of the genus *Tatusia* have to do and, as we have seen, *T. hybrida* makes one ovum go so far as to produce as many as a dozen embryos and *T. novemcincta* makes 4 as its normal litter.

It would be a matter of the greatest interest to know how widespread this business of producing more than one embryo from a single ovum may be in the mammals. Unfortunately the known facts are

so few that it is only possible to speculate on the subject. In the first place, before dogmatic statements could be made, it would be necessary to know precisely how many definite corpora lutea there were in the ovaries of the mother. In addition, the early stages of embryonic development would have to be definitely known and lastly the general likeness and identity in sex of resulting embryos would have to be ascertained. We do not know all these things concerning any of the mammals that might be considered likely to produce uniovular young.

It is, of course, only among the mammals that have gone some way towards the development of a single pregnancy type of uterus and a reduced series of mammary glands that we would be likely to find this method of producing multiple offspring. Two interesting classes therefore suggest themselves in this connexion—the volant mammals and the arboreal mammals. In both cases we know enough to make the question a tantalizing one, but one that cannot be solved by the facts so far available.

Concerning the volant mammals we have one very definite fact that is suggestive of further possibilities. Fortunately in his investigation into the reproductive story of the horse-shoe bat, Harrison Matthews recorded the fact that "*only one* (*corpus luteum*) *is present in each female*, in the right ovary and no corpora lutea atretica were found accompanying it." It is strange that all investigations into the anatomy of the Cheiroptera are agreed that only the right ovary has ever been found to contain a corpus luteum and only the right uterine cornu has ever been seen to contain the embryo. This would seem to be the most extreme case of the limitation of ovulation —that one ovary should be selected to produce the single ovum shed during ovulation. In the armadillos, although only 1 corpus luteum exists it may be found in either ovary, for both seem to be equally functional. The bats are not unique among the mammals in specializing in the functional activity of only one ovary. So far as is known, all the Monotremes, though possessing 2 ovaries and oviducts produce ova only from the left ovary. In these animals the selection is of the left sex gland, as is the case among birds, whereas in the bats it is the gland of the right side that alone functions.

Concerning the bats we also know that only a single embryo is ever produced by any species in Great Britain, But some species (such as the Pipistrell) which here produce a single offspring commonly have 2 in continental Europe. And here, just where the question becomes most interesting, our knowledge of facts ceases. So far as can be ascertained there is no record of the sex of the two offspring nor of the number of corpora lutea present in the ovaries of the mother. It is impossible to guess if the two young produced by the bats in France and Germany are uniovular or multiovular in origin.

Concerning the arboreal mammals there is the added interest that Man must be included in their number. Much light could be thrown upon this subject by a careful investigation into the reproduction of those monkeys that readily breed in captivity, for most monkeys occasionally produce 2 young at a birth. Facts as to the similarity or dissimilarity and the identity or difference in sex of the two young are necessary and, above all, the number of the corpora lutea, before any further advance can be made towards shedding light on the problem as it is presented by the lower Primates.

In the case of Man it must be admitted that our ignorance is almost complete and most of the accounts of the origin of human twins and multiple pregnancies are little

better than guesswork decked out in scientific trappings. In 1917 Newman wrote: "The evidence furnished by the *data* collected by obstetricians of twins *in utero* also favours the existence of monozygotic twins. Frequently this evidence is lacking in very essential points. Sometimes, for example, the sex is not mentioned, and never, so far as I am aware, is there information about the number of corpora lutea present. The importance of the latter *data* cannot be overemphasized in this connexion; a knowledge of whether one or more corpora lutea are present would furnish a crucial test of the number of ova concerned in a given pregnancy. *In not a single case of human multiple births, so far as I am aware, has the number of corpora lutea been noted.*" Failing this knowledge Newman pins his faith upon more scientific accounts of the conditions of placentation and disposition of the foetal membranes and he says: "Although *data* as to intra-uterine relations are incomplete and inconclusive, they form the only really direct evidence now available on the mode of twinning in Man." But even this evidence has to be treated with the greatest caution however scientifically it is recorded. In the case of *Dasypus villosus* we have seen how diovular embryos may by early readjustments of their foetal membranes in the confined space of a single-pregnancy uterus present every appearance of being monochorial twins.

What would seem to be most probable is that Homo, having produced a typical single-pregnancy type of uterus and a reduced series of mammary glands during the phylogenetic past, can in present circumstances of habit and environment face multiple pregnancies despite the initial anatomical handicap. Multiple pregnancies in Man may result from a reversion to the more primitive mammalian method of shedding several ova at an act of ovulation or it may be brought about by the armadillo's method of making more than one embryo from a single ovum. It is best to say that we have not sufficient evidence to determine which is the method most commonly employed. It seems safe to say that opposite-sexed pairs are certainly diovular in origin and that same-sexed pairs may or may not be uniovular. Even among the 4 uniovular foetuses of *Tatusia novemcincta* there is not absolute identity in all characters but there is a very definite and striking similarity between them. A very striking similarity between the 2 members of a same-sexed pair of human beings is strong presumptive evidence of their uniovular origin. Perhaps that is as far as it is safe to go and possibly it would be a gain to limit the term twins to human paired, same-sexed offspring that exhibit a high degree of general similarity.

The reason why it might be desirable to limit the term twins to what are commonly termed "identical twins" is that confusion with what are termed twins among lower animals would be avoided. When an animal which normally produces fairly large litters, produces only 2 young we do not commonly apply the term twins to them. We do not speak of twin rabbits if the mother chances to produce only two. But with such domestic animals as generally produce only one at a birth the occasional 2 that are begot are commonly termed twins. The use of this term opens up the old questions of twinning in Ungulates and the production of the freemartin.

John Hunter (1786), Numan, the Dutch veterinarian (1843), Spiegelberg in Germany (1861), Berry Hart (1910), L. J. Cole (1916) and F. R. Lillie (1916) are among the prominent workers who have helped to build up a vast literature on the subject of the freemartin. But the freemartin does not, as has been so commonly held, provide any evidence in favour of the

uniovular origin of ruminant twins. Lillie has shown quite conclusively that the freemartin is a female, aborted in the development of its proper female sexual characters, by the male hormone passing into its circulation, which has become confluent with that of the fully sexed bull with which it shares the uterus. It is impossible not to agree with the summing up of Lillie's work by Newman: "The work leaves no question as to the dizygotic origin, not only of opposite sexed, but also of same sexed bovine twins. Whether real monozygotic twinning ever occurs among the Ungulates is highly questionable."

So far as is at present definitely known the production of more than one embryo from a single ovum—or what might perhaps be properly termed twinning—occurs only in Man and the Armadillos of the genus *Tatusia*. It might be expected to occur at times in other Primates and in the Bats, but we should not look for it outside the limits of those animals that, having in the phylogenetic past reduced the uterus, the ovary and the mammary glands to the single-pregnancy type, find it possible, perhaps by changed circumstances, to be pregnant of and to rear more than one offspring at a birth.

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Full-time Intraligamentous Ectopic Gestation

BY

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THE intraligamentous type of tubal gestation is sufficiently rare to warrant the recording of details of every case. This becomes increasingly so in those few instances which succeed, despite the abnormal location of the gestation sac, in proceeding to term.

The case in question is that of a full-time anterior subperitoneal intraligamentous pregnancy which was discovered in one of the bodies sent to the dissecting room of this Department. The previous history, as obtained from departmental records, showed that the patient was a Sinhalese, 29 years old. This was her second pregnancy; the first resulting in a normal delivery 8 years ago.

I. PRELIMINARY EXAMINATION OF THE CADAVER.

The body was that of a very well nourished woman of average build; weight 100 pounds. On abdominal palpation a hard mass, thought at first to be a foetal head, was felt high up to the left of the middle line, and the foetal back on the right side.

An attempt to withdraw some amniotic fluid (by inserting a needle through the middle line below the umbilicus) for the purpose of injecting formalin, was a failure.

II. NOTES ON DISSECTION.

The body was opened by two paramedian incisions to avoid injury to the linea nigra which, despite the deep pigmentation of the general bodily surface, was very pronounced.

A horizontal incision was then made above the umbilicus and the flaps turned back.

1. *The gestation sac.*

A large thin-walled sac occupied the centre and right of the pelvis and lower abdomen. The thin wall of the sac was accidently penetrated by the knife and revealed the back of a full-time child whose buttocks were disposed upwards and to the right and whose head was later discovered well down in the pelvis in the right occipito-anterior position. Amniotic fluid was absent; the membranes lying on the surface of the child. The anterior (peritoneal) wall of the gestation sac was reflected along the inguinal region on the posterior aspect of the anterior abdominal wall. The stretched ligamentum teres extended across the sac towards the internal abdominal ring. The caecum and appendix were closely adherent to the top of the sac on its extreme right. The right Fallopian tube was found along the upper edge of the sac. The right ovary was normal and to the right of the tube, and above the sac.

2. *Uterus.*

This organ was displaced to the left and upwards and was enlarged to the size of a foetal head and hard to the touch. It was this object which had given the impression of a foetal head on abdominal palpation prior to anatomical exploration.

The following measurements were recorded:

Length - - - - -	6 inches.
Breadth - - - - -	4 inches.
Thickness of wall -	$1\frac{1}{2}$ inches.

A window dissection made on the anterior wall of the uterus showed that the head of the child was making its way through the side wall of the uterus at its junction with the cervix and the body of the uterus was pushed up and to the left, 'sitting,' as it were, on the head of the child.

On vaginal examination the cervix was found to be thickened and the os admitted one finger, but it was possible to meet a finger from the other hand placed in the pelvic extension of the gestation chamber, proving that an attempt had been made by nature to discharge the child into the natural passages.

Further dissection revealed that the aperture so formed in the right lateral fornix extended upwards affecting the right aspect of the cervical canal and also the right lateral wall of the lower uterine segment, but these deficiencies were closed by the placenta, which had gained attachment to the lateral uterine wall.

3. *Fallopian tubes.*

The left tube was normal in length ($3\frac{1}{2}$ inches), but was compressed, with the left ovary against the side wall of the pelvis by the enlarged and displaced uterus. The right tube was stretched to $4\frac{1}{2}$ inches. Its ampullary portion was thickened and swollen, the swollen part measuring 2 inches by $1\frac{1}{4}$ inches and opening below into the gestation sac, thus suggesting that this part of the tube was the primary location of the ovum.

4. *Placenta.*

After opening the gestation sac and withdrawing the foetus, the placenta was found attached to the medial half of the upper part of the anterior wall of the sac; passing thence on to the right lateral wall of the body of the uterus, between the two layers of the broad ligament. Its upper margin gained the Fallopian tube, but whether or not there was any original placental attachment, or alternatively, whether this was due to secondary extension, cannot be definitely stated. The area in contact with the uterine wall included the portion of the latter that had been eroded, producing the rupture already referred to in dealing with the uterus.

5. *Child.*

The child was a well developed, full time male of 18 inches crown-rump length, weighing 3 pounds $1\frac{1}{2}$ ounces. The umbilical cord measured $19\frac{1}{2}$ inches long.

Discussion.

All obstetrical authorities agree on the rarity of the secondary intra-ligamentous or mesometrial type of ectopic pregnancy. Eden and Lockyer[1] maintain that many, if not most, of the examples in the literature are not true intra-ligamentous pregnancies, but are subject to explanations other than that needed to produce the mesometrial location of the gestation sac, i.e. the rupture of the lower wall of a tubal gestation sac, whereby the foetal membranes are enabled to expand by separation of the two layers of peritoneum comprising the broad ligament, without rupturing them and becoming intraperitoneal. These authors

Photograph of pelvis with intra-ligamentous pregnancy at term. The gestation sac has been opened and the child removed and placed to the right of the patient. The umbilical cord is seen proceeding towards the placenta, which is still *in situ*. The uterus is seen to the left of the median line.

maintain that the rupture of blood vessels in this event would lead to haemorrhage sufficient to cause the death of the foetus; therefore examples which proceed to term cannot be regarded as due to this kind of tubal rupture. Jellet and Madill[2] on the other hand, aver that the support given by the layers of the broad ligament is such that any accompanying haemorrhage is limited. In any case, what usually happens apparently, is that the gestation sac, whichever way it comes to lie in the broad ligament, succumbs to the accident and a haematocele is the consequence. Nevertheless, it is generally admitted that individual instances can withstand the process and do occasionally carry on by virtue of the activities of the foetal membranes, whereby the placenta affixes itself to neighbouring tissues and draws therefrom sufficient nutriment for the foetus to survive till term. Many, however, undergo secondary rupture due either to stretching from foetal growth or to the erosive powers of the placenta. Such rupture may be into the general peritoneal cavity or into the genital passages; or occasionally both. These cases are attended by fatal consequences to the woman.

It remains to state why the present example is claimed as a true intra-ligamentous gestation, secondary to tubal pregnancy. This may be best accomplished by ruling out the other possibilities which are: (i) interstitial (tubo-uterine) pregnancy, (ii) ordinary tubal gestation, (iii) pseudo-ligamentous gestation. The first alternative seems to be the most likely and the secondary rupture into the right side of the uterus is somewhat in its favour. But against this explanation we have the fact that the gestation sac is not covered anywhere by muscle, nor does it show any evidence of the remains of uterine tissue over its surface, while the site of the rupture is too low down for a pregnancy commencing in the intramural portion of the tube. Moreover the anatomical appearances and the site of placental attachment suggest almost incontravertibly that the rupture has been due to erosion from without. Also the relations of the sac at term would necessitate the assumption that a double rupture, inwards and outwards, had occurred if the sac commenced its growth at the tubo-uterine junction—and, though such cases of double rupture are known, they are very rare.

It might be possible to explain some cases of apparent mesometrial location of a gestation sac to the continuance of an ordinary tubal gestation which had ruptured intraperitoneally and become secondarily covered with serous membrane derived from inflammatory tissues. This explanation is not very convincing, but might cover some examples where the peritoneum had not been stripped off the anterior abdominal and pelvic walls or the posterior wall of the cavity. As the stripping had occurred chiefly anteriorly in the present case, though not to such a degree as in Berry Hart's[3, 4] example, it is not considered that the explanation just given is adequate. Added to this is the fact that the peritoneum is comparatively undisturbed posteriorly, so that the gestation sac has a complete peritoneal covering, except where it is connected with the tube and lateral uterine wall. Moreover the dislocation of the uterus to the left is too great to be accounted for except by virtue of a true mesometrial site for the sac.

The pseudo-ligamentous gestation is rather a special variety of the preceding. It commences in the ampullary portion of the tube, which, instead of rupturing, becomes inordinately stretched over the growing sac contained within. As it stretches, the tubal wall becomes secondarily attached to the posterior layer of the broad ligament and so the sac appears to be contained within the latter. The prob-

able commencement of the pregnancy in the ampullary portion of the tube in the present instance is evidence in favour of this interpretation, especially when it is considered that true mesometrial pregnancy most usually starts in the isthmic region of the tube. But the ventral growth being the principal feature in the present case, argues against the diagnosis of pseudo-ligamentous pregnancy.

So we are left with the conclusion that we are dealing here with a true mêsometrial pregnancy. The pregnancy has proceeded to term and the erosive action of the placenta has produced a secondary opening into the birth canal. Lack of expulsive power around the wall of the gestation sac has resulted in the foetal head becoming impacted in the maternal pelvis; and the mother has died, not from haemorrhage so much as shock, although some haemorrhage from the lower part of the placenta was probably a precursor of this.

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REVIEWS OF HOSPITAL REPORTS

REPORT OF THE ROTUNDA HOSPITAL.

By the Master, Dr. Ninian McI. Falkiner, and the Staff of the hospital covers the year November 1st, 1942, to October 31st, 1943. Before passing to the substance of the report a fitting tribute is paid to the memory of the late Sir William de Courcy Wheeler, who had been consultant surgeon to the hospital for many years. The work reviewed has been carried out in the out-patient department, the district, the obstetric wards, paediatric department, gynaecological wards and Social service department.

At the out-patient department there were 38,223 attendances. Of these 15,313 were antenatal visits. Eighty-six per cent of the patients delivered in the hospital attended the antenatal clinic. Routine blood Wassermann reaction is once again advocated on all pregnant women. While the work done in the antenatal department gives great satisfaction, no efficient postnatal clinic has as yet been organized. It is thought that if this could be rectified by establishing a clinic to which both mother and baby could be referred on discharge from the hospital, more patients could be persuaded to continue with breast feeding. Breast feeding has been all too easily abandoned by patients in spite of a campaign in its favour.

The problem of under nourishment has been helped by the establishment of antenatal and postnatal dining centres in various parts of the city. Some 443 patients received meals during the year from these, but on the other hand there there were 5,420 deliveries in the hospital and its district. The 8th day of the puerperium is the customary day for discharge from the hospital. By this time breast feeding is rarely properly established and, as is so common, when the first difficulties are encountered the mother gives up the struggle and puts the baby on the bottle. The mother should really have another week in hospital. This problem is by no means confined to the Rotunda where the intern maternity turnover is steadily increasing year by year, reaching 3,884 deliveries in the year under review, from 2,773 in 1934. Longer stay in hospital is therefore impossible. Already overcrowding is serious, as reflected in the paediatric section. As with the child, so with the mother, overcrowding means infection. The Master's solution is that more women must be confined in their own homes, and the Rotunda would work for that end. As an immediate solution it may work. More and more, however, institutional confinement is being demanded by the populace, and not without reason. It is so much more convenient for many. As long-term policy surely sufficient accommodation should be provided for institutional deliveries, with adequate lying-in beds. This would allow the mother to have a proper rest, often sorely needed. It would then be possible for many feeding difficulties to be overcome while the patient was still under supervision.

In spite of the difficulties under which the hospital is working the report indicates a very high standard of achievement. Of 1,536 district deliveries, and 3,884 deliveries in hospital there were 11 deaths. (1 district, 10 hospital, giving a mortality rate of 0.257 per cent in the hospital, and for the combined service, 0.202 per cent. One death was considered due to haemorrhagic encephalitis following N.A.B. therapy. The patient was admitted unconscious 48 hours after the second injection (0.6 grm.—incidentally erroneously stated as 6 grm. on p. 118). She died 7 hours later. Reference is made to 4 other patients whose lives were imperilled. Dr. Falkiner has abandoned the use of arsenicals in the treatment of syphilis in pregnant women and is at present using bismuth. The remaining hospital deaths are critically reviewed and there is nothing to add. The district fatal case was somewhat unusual and considered to be primarily due to malnutrition.

In breech delivery the test of skill is the delivery of the full-time child in the primigravida where there is no other obstetric abnormality. To arrive at this figure was not easy, but the over all foetal mortality is not high.

The induction of labour table shows an unusual feature—surgical induction was performed for 21 cases of dead foetus, while only in 3 cases of dead foetus was drug induction used. Induction of labour was not carried out in any case of sus-

pect disproportion in a primigravida it is stated. Of 10 2nd gravidae, however, 3 had had the first labour induced at 39 weeks: 1 in the first pregnancy had been going to have a Caesarean section, but the foetus died *in utero*, and a 4-pound child was born as a result of a drug induction. In 4 cases, therefore, in 2nd gravidae, induction was performed when it was not known by trial what the patient could do if given a chance. One remarkable case (B.B.5/5/43) is that of a 19th gravida with a flat pelvis who had had 3 previous lower segment Caesarean sections and was admitted with a transverse lie and ruptured membranes but without pains. Pains were induced by bringing a leg down through a 2-finger cervix. She was delivered of a living baby weighing 7 pounds 6 ounces.—"Head difficult by Smellie-Veit." This case is illustrative of the attitude towards Caesarean section. This operation is avoided so much that one is inclined to think that occasionally zeal outruns judgment. The Caesarean section rate is approximately 1.7 per cent. Of 45 Caesarean sections of which details are given 3 had spinal, 3 general, and 2 local anaesthetics, while in 37 details of anaesthetics are not given.

In the toxaemic section there were 250 cases (6.4 per cent). The incidence of albuminuria is fairly high (181), while the remainder are classified as "eclampsism" (21), "eclampsia" (24), "nephritic toxaemia" (15), and hypertensive toxaemia (11). It would be interesting to know what is the standard of hypertension. In the patient of 46 years with hydatidiform mole and "eclampsia" (A.G. 29/9/43) hysterectomy without opening the uterus would have avoided a number of complications.

In the Paediatric Department there has been trouble. The general paediatric lay-out in the hospital is outlined. Epidemic after epidemic of gastro-enteritis has taken place in the hospital as in Dublin itself. Inadequate nursing, out of date and hopelessly inadequate accommodation for babies are responsible factors. Immediately required are a special isolation department for babies, additional nursing and medical supervision. All told there were 144 neonatal deaths. Twenty-two full-time normal healthy babies died of enteritis. An important observation is that not one of the babies who contracted enteritis and died was either wholly or partially breast fed. Such is the position frankly and critically stated in the report.

The work of the pathological and gynaecological departments is briefly outlined.

The Master and Staff have much of which to be proud. Where results could be criticized adversely they have done so themselves and pointed out the remedy.

CLINICAL REPORT OF THE COOMBE LYING-IN HOSPITAL.

THIS is Dr. Edward A. Keelan's first report as Master of the Coombe Hospital, and covers the period December 17th, 1942, to December 31st, 1943.

The hospital's capacity has been taxed to the full and sometimes overtaxed. More lying-in beds are required. There were 1,877 intern deliveries, and 1,433 district deliveries, making 3,310 deliveries in the hospital service. There were 6,739 attendances at the antenatal clinic.

In intern practice there were 6 deaths among delivered patients, 2 died undelivered of cerebral haemorrhage and 1 died of B. coli septicaemia 14 days after transfer (16 days after delivery) to a fever hospital, giving a total of 9 deaths (0.49 per cent). One patient died in the district service. This gives a total maternal mortality of 0.3 per cent in the complete hospital practice. In calculating these mortality rates I have included the 2 deaths in the undelivered patients and also the death of the transferred patient. To exclude them as is done in the opening summary of the report is to exclude 33⅓ per cent of the intern maternal deaths in the service from the calculated mortality rate.

Of these fatal cases there is an instructive case of marginal placenta praevia (308/43). She was admitted at 33 weeks bleeding slightly. Vaginal examination under anaesthesia revealed marginal placenta praevia but treatment was not carried out. Because she lived near by and did not bleed for the next 5 days she was allowed to go home, having been told to report or send for help immediately should bleeding recur. She failed to carry out this advice when bleeding did recur 2 weeks later. Four hours after the onset of bleeding she arrived in the hospital moribund. (Every obstetrician who has treated antepartum haemorrhage expectantly in

hospital must, upon occasion, have cast a longing eye on a much needed bed occupied by an apparently healthy woman who was being kept in hospital merely because she had a slight painless haemorrhage. It is difficult at times to be fully persuaded that such a woman is in imminent danger of death. Yet she is.) One might wonder, if expectant treatment was contemplated, why the examination under anaesthesia on admission? This is not an isolated instance of examination under anaesthesia with detection of placenta praevia and then the adoption of expectant treatment. In case 468/43 the same was done. This practice would seem to invite further bleeding when the evidently desired expectant treatment would have to be abandoned. It has been said that there is a place for the expectant treatment of antepartum haemorrhage, but not for the expectant treatment of placenta praevia.

Turning to the other cases of placenta praevia we find 5 cases of central placenta praevia in which the treatment was "Foot brought down." In none of 19 cases of placenta praevia was Caesarean section performed. There was only 1 maternal death, but out of 17 cases in which the baby weighed 5 pounds or over, there were 7 stillbirths (41 per cent). It is gratifying to note that the Master has stated that his preference is now for lower segment Caesarean section "in those cases of central and marginal placenta praevia, which have been diagnosed under aseptic conditions, and in which the baby weighs approximately 6 pounds or upwards."

Among 9 cases of prolapsed umbilical cord there were 5 living children. Of 4 stillbirths 2 had died *in utero* before admission, 1 was deformed and the mother of the remaining 1 had severe pre-eclampsia. Congratulation is due for successful result to mother and child by lower uterine segment Caesarean section in a primigravida at term (1111/43) with a free disproportionate head, the forceps having been applied outside while the cervix was only one-quarter dilated; there were 5 inches of prolapsed cord in the vagina. What is meant by Case 9 of this table (1504/43) I do not know. "Breech" is stated as the complication of this case of prolapsed cord. The treatment (for the prolapsed cord) is stated as "version." The case does not appear in the table of internal and combined version. Presumably, therefore, the version was external, and cephalic (the presentation is stated as breech). Yet in the remarks we find "Grav. 7. Aet. 39. Footling presentation. Os full. Extraction."

The mid-forceps rate is 1.5 per cent. When low forceps cases are added, the total forceps rate is 6 per cent. The induction of labour rate is low. There were 6 drug inductions, nearly all for dead foetuses. There were 23 surgical inductions of which 2 were for the prevention of dystocia while the remainder were for a variety of commonly accepted indications and a number of toxaemic cases. The method of surgical induction, however, is usually not stated. Of 23 inductions the method is stated only in 3, and a different name is given in each case for the same method, and by implication a fourth case was induced similarly by puncture of the membranes. How were the remaining 19 induced?

There were 19 cases of new Caesarean section. Disproportion was the main indication in 11, all of which had been in labour for some time. Three of the 19 became morbid on the B.M.A. standard, and in addition 1 died of peritonitis. All 23 repeat Caesarean sections were performed for disproportion. Two of those had each had 6 previous sections, and 1 had had 5 previous sections. All the babies of the new Caesarean sections survived. Among the repeat sections there were 2 neonatal deaths. In one of these there was difficulty in extraction of the foetus on which autopsy showed a small tentorial tear and congestion of the viscera: in the second where the cause of death is not stated, the baby weighed 6 pounds 8 ounces, and the anaesthetic had been open ether.

Accidental haemorrhage occurred in 17 cases. Among these were 1 maternal death, 10 stillbirths, and 1 neonatal death. In general the initial treatment was conservative, treating shock and if necessary, replacing blood loss. Where the cervix was partly dilated and being taken up the membranes were punctured. Repeated small doses of morphine were given for the relief of pain. The table does not state definitely whether the patients were in labour or not when they came under observation. By deduction the majority were in labour. Case 8 (471/43) presumably was not in labour, for the cervix was closed and had to be dilated before the membranes could be punctured. Yet this case does not appear in induction of labour tables.

Case 1 (90/43) a primigravida 28 weeks pregnant on admission, is said to be 52 years old. That so unusual an occurrence should pass without comment suggests that the stated age may be a misprint.

The maternal deaths, on the whole, are clearly set out in their own table and some critical comments are made on these in the opening survey (page 3) of the report. The description of case 1659/43 is difficult to follow in the Caesarean section and mortality tables, but when read in conjunction with para (3) on page 3 the picture becomes clear.

The morbidity rate of 2.2 per cent on the B.M.A. standard is very satisfactory.

Extern maternity details are set out on one page by themselves. There was 1 maternal death from uterine infection. Twenty-three children were stillborn (2 macerated) and neonatal deaths were 16.

A list of 387 gynaecological operations performed follows, with details of 3 fatal cases. Notes on the work of the pathological and Almoner's department bring the report to a close.

While certain criticisms have been expressed, this report reveals a high standard of obstetric practice, in which the guiding hand is that of a highly trained conservative obstetrician. The Master is to be congratulated on his first year's work, in which he has upheld the great Irish tradition.

MEDICAL AND CLINICAL REPORT OF THE ELSIE INGLIS MEMORIAL MATERNITY HOSPITAL, EDINBURGH,

FOR THE YEAR 1943.

THIS report is of a different plan from the two former ones. The survey of the year's work is considered under customary headings. The tables show the total number of cases within each major group with numerical results, which are frequently subdivided also numerically, but in no group are detailed clinical *data* of single cases recorded. There is, however, a lot of information in this report.

There were 1,310 deliveries (including 25 abortions) in the hospital and 552 deliveries (including 25 abortions) on the district, making a total of 1,862 deliveries (including 50 abortions), in the complete service. A differentiation is made between "Booked" and "Unbooked" cases. The relation of the former to the latter is roughly 35 to 1.

The maternal mortality in the complete service was 3 deaths—2 in the hospital and 1 in the district practice. Both hospital cases were "Booked." In one death was ascribed to asphyxia from the inhalation of vomit during anaesthesia (gas and oxygen), and in the other to shock following craniotomy for obstructed labour due to deflexed head and compound presentation. The "unbooked" district fatality occurred from valvular disease of the heart. This patient had mitral stenosis with decompensation, and premature (twin) labour set in at 28 weeks. She died 24 days later in a general hospital. Maternal morbidity was 3.7 per cent on the B.M.A. standard, or 2.8 per cent notifiable pyrexia standard. The stillbirth-rate was 38 per 1,000 viable births, and the neonatal mortality 31 per 1,000 live births.

The section dealing with the treatment of antenatal abnormalities is straightforward. It would be helpful to the reader, however, to know what are the standards for the diagnosis of pre-eclampsia. (This applies to all the hypertensive toxaemias in all these reports, because the standards and practice adopted vary so much from hospital to hospital.) Similarly some explanation of the conditions governing the admissions to the department for venereal diseases and vaginal discharge ("L" ward) might have been included. It is stated that 120 adults, and 47 babies suffering from ophthalmia neonatorum, were admitted to "L" ward. Of the 120 adults 20 had syphilis, 9 had gonorrhoea and 91 had non-venereal vaginal discharge requiring in-patient treatment. Some of these figures seemed high for a hospital with 1,310 (including 25 abortions) in-patient deliveries. Inquiry from the hospital reveals that the department for venereal disease is part of the general scheme for the city. Practically all pregnant women, from the city and surrounding regions, requiring treatment are referred to one of two voluntary maternity hospitals of which this is one. This explains the figures for adults. Of the 91 patients with non-venereal vaginal discharge there were in fact 57 admitted for treatment while the remainder (34) were treated as out-patients. As regards the ophthalmia neonatorum figures, these include

"every infant up to the age of 21 days showing any discharge from the eyes however slight." Provision is made for the admission from the district of babies requiring observation. The figure of 47 cases of ophthalmia in hospital cases is a mistake. It should read 34, the rest being district cases. Two of the ophthalmias were gonococcal (1 born in the hospital and 1 outside): neither was severe it seems.

In the breech presentation table the method of arriving at the corrected foetal mortality rate is not clear. Among obstetric operations 3 cases of high forceps (indication prolapsed umbilical cord) are noteworthy. The term high forceps is not often seen now. It is a pity we have not the details of single cases. There were 58 Caesarean sections (13 repeat operations) with, after the exclusion of 2 monsters, a corrected foetal mortality rate of 10 per cent. An unusual indication, for which 4 emergency sections were performed, is the not very explicit term "non-polarity." Induction of labour was carried out on 217 occasions. In 116 cases a combination of medical induction and artificial rupture of membranes was used, medical alone in 87, oestroform in 6 and balloon induction in 8 cases. Impending disproportion was the indication in 9 cases, but we are not told whether in primigravidae or multiparous patients. It is open to question whether "social and economic reasons, difficulty of transport, conservation of beds, etc." are justifiable indications for 36 combined (medical and artificial rupture of membranes) inductions. There were 59 cases of postpartum haemorrhage or shock. Transfusion of blood or plasma was given on 19 occasions, and the placenta was removed manually in 16 cases.

There is also a bacterial report. It seems that swabs are taken from the fauces and lower part of the vagina in all patients: (*a*) on admission to the antenatal or labour wards and (*b*) on the 4th day of the puerperium. Swabs are taken from the cervix before surgical induction is undertaken. The incidence of haemolytic streptococci in the various sites is given. Lancefield grouping is not indicated. We are told, however, that in 14 cases in which the occurrence of haemolytic streptococci was associated with genital infection none was Group A.

In the paediatric section there are many interesting figures. It would be helpful to know whether specified causes of stillbirth and neonatal death had been confirmed by postmortem examination.

The reading of this report leaves the impression that it is one of possibilities and potentialities. It tells a lot, but prompts many questions. Could it be expanded by single case *data* in its various sections it would be a splendid report.

Detailed clinical reports are most important documents. From them much can be learned, both by those who produce them and by those who study them. When reports from a large number of hospitals over a period of years are collected we have one of the simplest forms of access to large numbers of cases for the study of individual conditions and diseases. Yet they can be disappointing, and their value impaired if the results of one hospital are not comparable with those of another. I should like to plead for more uniformity in the plan of these reports. Surely it ought to be possible to agree on the tables which it is desirable to include in a report. One hospital gives detailed tables of postpartum haemorrhage, manual removal of placenta, trial of labour, primary uterine inertia, etc. and others do not. From those who do not the figures we desire to know may be arrived at by complex searching of other tables and laborious calculation and even then we may be frustrated. There is not agreement on the *data* which should be recorded in the tables which are set out in detail. There is not even agreement on what is meant by terms such as complicated, and uncomplicated breech. Since the last meeting of the Royal Society of Medicine devoted to such Reports a number of years has passed and there have been changes in practice. Hospitals which have cut down their reports to a mere skeleton because of paper shortage and curtailed staff, must be thinking ahead to the time when they can re-expand them once again.

Should not that day of re-expansion be the time for more uniformity and comparable *data*? Should the Obstetrical division of the Royal Society of Medicine devote another meeting to it or should the Royal College of Obstetricians and Gynaecologists prepare what it considers an ideal form of Annual Clinical Report?

ANTHONY W. PURDIE.

BOOK REVIEW

"The South African Frog (Xenopus laevis) in Pregnancy Diagnosis." Weisman and Coates. THE sub-title of this book describes it as a research bulletin. In fact, it is mainly a semi-popular account of investigations undertaken largely by Hogben's school between 1930 and 1941 and repeated with some embroidery by the authors between 1942 and 1944.

The book performs a useful service in collecting together most of the published knowledge concerning Xenopus, including a comprehensive bibliography and details of the animals' habitat, anatomy and behaviour. It is chiefly concerned with Xenopus as a test animal in pregnancy diagnosis though the style adopted results in the inclusion of much irrelevent detail. Instructions are given for maintaining stocks of Xenopus and for carrying out the test. One serious fault in their technique is in extraction of the urine prior to testing. The method they recommend was discarded by British workers in 1941 after that published by Scott had been tested and proved. Weisman and Coates, however, condemn Scott's method without trial, claiming 98.9 per cent accuracy in 1,000 cases as against Scott's 100 per cent accuracy in 1,000 cases. An interesting table summarizes the experiences of about 20 groups of workers who have used the animal for pregnancy diagnosis. In the last 10 years nearly 7,000 tests have been recorded with accuracies varying with the worker from 96 per cent to 100 per cent. The authors point out, and give details showing, that the test is accurate, speedy, inexpensive and simple to perform and that the animals are easier to maintain than laboratory rodents. As they summarize: Xenopus has "earned its rightful place in the world of science. It should rank on the same and equal plane with the guinea-pig, the rabbit and the rat."

F. W. LANDGREBE.

INDEX TO CURRENT LITERATURE

In this Index an endeavour will be made, so far as war conditions permit, to maintain an up-to-date record of all titles bearing on obstetrics and gynaecology and the infant. The classification aims at making immediately available for the reader the titles under the various subject headings. In the majority of instances the title is obtained from the original publication. Where this has been impossible, the title has been obtained from the abstracting journal shown in brackets. Reprints will be welcomed and should be sent to the Editor.

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